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URIC ACID

The Chemistry, Physiology, and Pathology of Uric Acid

AND THE

Physiologically Important Purin Bodies

WITH A DISCUSSION OF

THE METABOLISM IN GOUT

BY

FRANCIS H. McCRUDDEN

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INTRODUCTION

Four years ago the author began a study of the metabolism in certain chronic bone diseases, — rheumatoid arthritis, osteo-arthritis, osteitis deformans, etc., — under the direction of Doctors Goldthwait, Painter and Osgood, of Boston. After some preliminary chemical work it seemed advisable to make a very thorough study of the literature concerning the metabolism of the inorganic elements, and also of uric acid, since in the opinion of certain writers uric acid is of great importance in the etiology of the rheumatic diseases. The results of this study led to the conclusion that rheumatic diseases and uric-acid metabolism do not, at the present time, seem to be closely related. The fact that many English writers do not agree with this conclusion, and that there is no complete and reliable account of the metabolism of uric acid to be found in one place, made it seem advisable to publish the results of the work.

The view of Haig,[1] the foremost of those who attribute to uric acid a great pathological importance, may be seen from the following extracts. On page 10 he says: " Uric acid affects not only the blood, but influences in a similar way the functions, nutrition, and eventually the structure of every organ and tissue in the body, and as regards infectious diseases has, in some cases, a more important influence than the microbes themselves. As regards the tissues, it controls the production of energy and the production of heat to an extent which, acting as it does from bone to bone throughout the whole of life, cannot but be of enormous importance! But more recent advances have carried us far beyond this, and we can now say with absolute certainty that uric acid controls and conditions the capillary circulation of the whole body, . . . and thus regulates the blood pressure, the heart action, the nutrition of the heart and vessels, the nutrition of the tissue, and all the metabolic phenomena which constitute the life of the body to its minutest cells." And again, on page 168, he says: " Uric acid really dominates the function, nutrition, and structure of the human body, to an extent which has never yet been dreamed of in our philosophy, and in place of affecting the structure of a few comparatively insignificant fibrous tissues in which it is found after

[1] A. Haig. Uric Acid as a Factor in the Causation of Disease. 6th ed., 1903.

death, it may really direct the development, life, history, and final decay and dissolution of every tissue, from the most important nerve centers and the most active glands, to the matrix of the nails and the structure of the skin and hair."

I think any one who reads this book cannot but come to the conclusion that Haig's views are entirely unwarranted.

The time, too, seemed ripe for such a publication. Although the metabolism of uric acid is by no means completely understood at the present moment, yet several researches have recently been carried out which settle many points of fundamental importance in the theory of uric-acid metabolism and gout. Therefore, it seemed advisable to define the present status of the subject. Among these researches may be mentioned the two publications of Burian and Schur in 1901. These authors have shown quantitatively that it is the purin bodies of the food, either free or combined in nuclein, and only the purin bodies, that have any influence on the excretion of exogenous uric acid. They also showed quantitatively the relative importance of the endogenous and exogenous uric acid. Fischer's paper on the purin bodies in 1899, makes clear why the purin bases should be of such importance in uric acid metabolism. His has recently applied the methods of the science of physical chemistry to the determination of the behavior of uric acid in solution. As a result of his work, many of the old views concerning the solubility of uric acid in water and in the urine, and the effects of alkalies and other agents on the solubility of uric acid, have been overthrown. Physical chemistry has taught us that the acidity and the alkalinity of many solutions of complex mixtures of electrolytes such as blood and urine cannot be determined by titration methods. Only recently has an accurate method been offered by which we could determine the acidity of the urine and the alkalinity of the blood. By means of this method Höber has shown that the prevailing views concerning the acidity of the urine and the alkalinity of the blood are far from correct. The work of His and Höber, taken together, puts an end to many theories concerning uric acid in the blood and urine, and to any scientific basis for the alkali therapeutics in gout. Another point of importance only recently established by Burian and Schur, Soetbeer and Ibrahim and Salkowski, is the fact that uric acid is excreted in great part unchanged by man. This is certainly a final death-blow to the old view that uric acid is an antecedent of urea in the destructive metabolism of proteid.

I have made a thorough study of the pure chemistry of uric acid, and of its decomposition products, and of those purin bodies which have physiological importance; of the behavior of uric acid in solutions of pure water; in the solution of simple and mixed electrolytes, and of organic compounds;

and in the urine and blood. I have attempted to study all the research that has been done on the physiology of uric acid, the effects of food, and of the qualitative and quantitative change in the food, the effects of alcohol, exercise and other physiological functions, and also the research on uric acid in pathological conditions of all kinds, especially in gout. I have also studied the work on the general metabolism in gout.

I have arranged the material systematically, going from the simple facts of the pure chemistry of the purin bodies to gradually more complex conditions of metabolism, so that by the time the section on the metabolism in gout has been reached, all the facts upon which different theories of gout are based have already been treated in the proper place. I have adhered closely to an exact statement of experimental data throughout, and have ventured in but few cases to propound a theoretical explanation of the facts, relying on the arrangement of the facts themselves to bring out the explanation.

I wish to thank Doctors Goldthwait, Painter and Osgood, who have undertaken all the expenses of the preparation and publication of this work.

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Harvard Medical School.

AUGUST, 1905.

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THE CHEMISTRY, PHYSIOLOGY, AND PATHOLOGY OF URIC ACID

I. The Pure Chemistry of Uric Acid and Some of the Physiologically Important Purin Bases

Purin and its derivatives have been called the nuclein bases by Kossel, the alloxuric bases by Krüger. The two latter have called the bases and uric acid together the alloxuric bodies. Fischer calls them all purin bodies, and this is probably the most common name for them now.

Since uric acid and the purin bases have been thought to be intimately connected with the subject of gout and the uric acid diathesis, it is of importance first to know something about the chemistry of these bodies.

General Chemical Behavior of Uric Acid and Purin Bases

The General Chemistry of the Purins

HISTORICAL

The Work of Scheele. — Uric acid was discovered in 1776 in bladder stones and human urine by Scheele.[1] He showed its acid nature by dissolving it in alkali and lime water. He obtained it pure by precipitation from its salts with weak acids. On dry distillation, carbon, ammonium carbonate, and a volatile acid gas (cyanuric acid), easily soluble in water, were obtained. Boiling hydrochloric acid had no action on it. Strong sulphuric acid decomposed it with formation of carbon dioxide and sulphur dioxide. Silver nitrate gave a black precipitate with an alkaline urate. Nitric acid or aqua regia dissolved the

[1] K. W. Scheele. Examen chemicum Calculi urinarii. Opuscular II, 73. Also, Lorenz Crell. Die neuesten Entdeckungen in der Chemie, III, 227.

acid with effervescence. These are the most important changes which uric acid undergoes.

From Scheele to Liebig. — At the same time and independently of Scheele, Bergmann [1] found uric acid in bladder stones.

Fourcroy [2] studied the physical properties of uric acid more accurately and named it first acide lithique, and later acid urique. He was the first [3] to find that chlorine water changes uric acid to urea, and observed the formation of hydrocyanic acid by the distillation of uric acid.

The discovery of uric acid in gouty concretions was made by Pearson,[4] although Neumeister [5] credits the discovery to Wollaston.

Somewhat later, Fourcroy and Vauquelin [6] found it in the excrement of birds. Guano is still the cheapest source for the preparation of this acid.

In 1815 William Prout [7] found the excrement of the boa constrictor to consist of 90 per cent uric acid partly combined with ammonia and potassium. Since then serpent excrements have furnished the best source for obtaining small amounts of uric acid.

In 1817 " xanthin oxyd " (xanthin) was discovered in bladder stones by Marcet.[8]

In 1820, Runge,[9] and in 1821,[10] Robiquet, Pelletier, and Caventou discovered caffein. Thein was discovered by Oudrey [11] in tea

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[1] T. Bergmann. Opuscular, IV, 387. And Crell. Die neuesten Entdeckungen in der Chemie, III, 232.

[2] A. Fourcroy. Annales de Chimie, 16, 113 (1793). Suite de L'Analyse. Comparée des différents espèces de Concrétions animales et végétales: tirée du Dictionnaire encyclopedique, art, calculs. *And* Examen des expériences et des observations nouvelles de M. G. Pearson sur les Concrétions urinaires de l'homme et comparison des résultats obtenus par ce chimiste avec ceux de Scheele, de Bergmann, et de quelque chimistes français. Annales de Chimie, 27, 225 (1798).

[3] Annales du Museum, 1, 98 (1802). Sur le nombre, la nature, et les caractère distinctifs des différents materiaux qui forment des calculs, les bézoards et les diverses concrétions des animaux.

[4] Pearson. Philosophical Transactions of the Royal Society, London. 15 (1798).

[5] Neumeister. Lehrbuch der physiologische Chemie. 2t Aufl., 681.

[6] Fourcroy et Vauquelin. Annales de Chimie, 56, 258 (1805). Sur le guano ou sur l'engrais natural des îlots de la mer du Sud près des côtes du Perou.

[7] Thomson. Annals of Philosophy, 5, 413. Analysis of the Excrements of the Boa Constrictor.

[8] An Essay on the Chemical History of Calcal Disorders. London, 1817.

[9] Runge. Phyto-chemische Entdeckungen. Berlin, 1820.

[10] Berzelius Jahresberichte, 4, 180 (1825), and 7, 269 (1828).

[11] Oudrey. Thein, eine organische Salzbase in Thee. Mag. für Pharm., 19, 49 (1827).

in 1827, and thein and caffein were shown to be identical by Jobst [1] in 1838.

Prout and Brugnatelli [2] studied carefully the decomposition of uric acid by nitric acid and discovered a colorless crystalline compound (alloxan) which they called acido-ossieritrico.

In 1829, Wöhler [3] showed the identity of the acid which Scheele had obtained by the dry distillation of uric acid and which had been called brenzblasensteinsäure or brenzuric acid (pyrouric acid) with the cyanuric acid prepared by Serullas [4] out of cyanuric chloride and confirmed the view of Fourcroy and Vauquelin [5] that urea was formed at the same time. He found that about half the distillate consists of urea and about half of cyanuric acid.

Liebig [6] and Mitscherlich [7] at about the same time first showed the elementary formula of uric acid to be $C_5H_4N_4O_3$.

The Work of Liebig and Wöhler. — From 1834 to 1838 Liebig and Wöhler worked together on uric acid. By oxidation with lead peroxide they showed the change of uric acid to allantoin, which substance had already been found in the amniotic fluid of the cow.[8] They showed the change of uric acid to alloxan by moderate oxidation, which had been previously described by Brugnatelli, and determined its composition by accurate analysis. They obtained and to some extent studied the properties of alloxan, alloxantin, dialuric acid, alloxanic acid, thiouric acid, uramil, parabanic acid, oxaluric acid, mesoxalic acid, mycomelinic acid, dialuric acid, uramilic acid, and xanthic oxide. They closed their work with a study of murexid, which Prout had first prepared and named ammonium purpurate. The results of their work appeared in 1838.[9]

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[1] C. Jobst. Thein identisch mit Caffein. Liebig's Ann. der Chem. u. Pharm., 25, 63 (1838).

[2] Giornale di Fisica, Chimica, etc., di Brugnatelli, 11, 38, and 117. Osservazioni sopra varj cangiamenti che avvengono nell' ossiurico (ac urico) trattato coll' ossisettonoso (ac nitroso).

[3] F. Wöhler. Poggendorf's Annalen der Physik und Chemie, 15, 619 (1829). Ueber die Zersetzung des Harnstoffs und der Harnsäure durch höhere Temperatur.

[4] Serullas. Doppelt. Chlorcyan, eine neue Verbindung des Chlors mit Cyan, und Cyansäure. Poggendorf's Annal., 15, 443 (1828).

[5] Fourcroy und Vauquelin. Neue Erfahrungen über den Harnstoff. Journal für die Chemie Physik und der Mineralogie, 6, 409 (1808).

[6] J. Liebig. Analyse der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 10, 47 (1834).

[7] Mitscherlich. Analysen kohlenstoffhaltiger Verbindungen. Poggendorf's Annal. d. Physik und Chemie, 33, 331 (1834).

[8] Buniva und Vauquelin. Ann. de Chimie, 33, 269 (1799). Sur l'eau de l'amnios de femme et de vache.

[9] F. Wöhler und J. Liebig. Liebig's Ann. der Chem. u. Pharm., 26, 241 (1838). Untersuchungen über die Natur der Harnsäure.

From Liebig to Emil Fischer. — During the next twenty-five years we have the work of Schlieper [1] on hydurilic acid and dilituric acid, that of Wosresensky,[2] who discovered theobromin; of Unger [3] who discovered guanin, which had previously been thought identical with xanthin; of Rochleder, who studied caffein [4] and theobromin,[5] and some of their derivatives; of Strecker, who discovered the change of guanin to xanthin by the action of nitrous acid [6] and the relations between guanin, xanthin, theobromin, caffein, and creatinin.

Strecker [7] was the first to change theobromin to caffein by the action of HI on the silver salt of theobromin. He obtained caffeidin by the action of barium hydroxide on caffein.[8] He studied the action of sodium amalgam on allantoin [9] and the decomposition of uric acid into carbon dioxide, ammonia, and glycocoll,[10] a decomposition which gave Horbaczewski a hint to the first synthesis of uric acid.

In 1843, Stenhouse [11] studied the thein from tea. In 1851, Stadeler studied uroxamic acid and uroxil. The work of Unger [12] in 1845 on xanthin and some of its compounds, and that of Scherer[13] on the guanin, hypoxanthin, and xanthin in horse flesh and the pancreas conclude the important work up to the time of Bæyer.

Bæyer's work gave the first clew to the constitution of many members of the uric acid group. He studied pseudouric acid,

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[1] Schlieper. Ueber Alloxan, Alloxursäure, und einige neue Zersetzungsprodukte der Harnsäure. Liebig's Ann. der Chem. u. Pharm. 55, 251 (1845).

[2] A. Wosresensky. Ueber das Theobromin. Liebig's Ann. der Chem. u. Pharm., 41, 125 (1842).

[3] Unger. Bemerkungen zu der Notiz von Einbrodt über die Zusammensetzung des Harnoxyds. Liebig's Ann. der Chem. u. Pharm., 58, 19 (1846).

[4] Rochleder. Ueber das Caffein. Liebig's Ann. der Chem. u. Pharm., 71, 1 (1849).

[5] *Ibid.* Liebig's Ann. der Chem. u. Pharm., 79, 124 (1851). Die Oxydationsprodukt des Theobromins, und über die Zusammensetzung der Rubiaceen.

[6] Strecker. Ueber der Verwandlung des Guanins in Xanthin. Liebig's Ann. der Chem. u. Pharm., 108, 141 (1858).

[7] *Ibid.* Untersuchungen über die chemischen Beziehungen zwischen Guanin, Xanthin, Theobromin, Caffein, und Kreatinin. Liebig's Ann. der Chem. u. Pharm., 118, 151 (1861).

[8] *Ibid.* Ueber die Zersetzung des Caffeins durch Barythydrat. Liebig's Ann. der Chem. u. Pharm., 123, 360 (1862).

[9] *Ibid.* Ueber einige Reduktionsprodukte des Allantoins und der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 131, 119 (1864).

[10] *Ibid.* Bildung von Glycocoll aus Harnsäure. Liebig's Ann. der Chem. u. Pharm., 146, 142 (1868).

[11] J. Stenhouse. Ueber Thein und seine Darstellung. Liebig's Ann. der Chem. u. Pharm., 45, 366 (1843), und Nachträgliches über das Thein. Liebig's Ann., 46, 227 (1843).

[12] Unger. Ueber das Xanthin. Liebig's Ann., 65, 222 (1845).

[13] Scherer. Ueber Hypoxanthin, Xanthin, und Guanin im Thierkörper und das Reichthum der Pancreas-drüse an Leucin. Liebig's Ann. der Chem. u. Pharm., 112, 257 (1859).

hydurilic acid and its salts,[1] violuric acid, dilituric acid and their salts, violantin, and alloxanbromid.[2] He made a special study of the alloxan derivatives,[3] and of nitromalonic acid, meso-oxalic acid, and some of their derivatives.[4]

Other articles of about this time deserving mention are the works of Rosengarten and Strecker on the action of barium hydroxide on caffeidin [5]; that of Hill on methyl uric acid [6]; of Phillips [7] on derivatives of caffein and theobromin; Mulder's work on the synthesis of barbituric acid and other ureides [8]; that of Drygin on ethyl derivatives of uric acid [9]; of Grimaux [10] on uric acid derivatives, and of Hill and Mabery [11] on the ethers of uric acid. Most important, perhaps, of all is the article of Medicus [12] on the constitution of the purin bodies. He proposed for uric acid and some of its derivatives the formulæ which Emil Fischer afterward proved to be correct.

STRUCTURE AND SYNTHESIS OF THE PURINS

Structure. — Horbaczewski first synthesized uric acid by melting together glycocoll and urea,[13] and later by melting together urea and the amide of trichlorlactic acid.[14] Behrend and Roosen [15] synthesized it from acetoacetic acid and urea. They first obtained methyl uracil, then isobarbituric acid, and finally

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[1] A. Bæyer. Untersuchungen über die Harnsäuregruppe. Liebig's Ann. der Chem. u. Pharm., 127, 1 (1863).

[2] *Ibid.*, 127, 199 (1863).

[3] *Ibid.*, 130, 129 (1864).

[4] *Ibid.*, 131, 291 (1864).

[5] F. Rosengarten und A. Strecker. Ueber die Spaltung des Caffeidins durch Barythydrat. Liebig's Ann. der Chem. u. Pharm., 157, 1 (1871).

[6] H. Hill. Ueber die Aether der Harnsäure. Ber. der Dtsch. chem. Gesell., 9, 370 (1876).

[7] L. Phillips. Notiz über eine dem Caffein homologe Base. Ber. der Dtsch. chem. Gesell., 9, 1308 (1876).

[8] Mulder. Beitrag zur Kenntniss der Ureide. Synthese von Dimethylbarbitursäure. Ber. der Dtsch. chem. Gesell., 12, 465 (1879).

[9] Drygin. Jahresber. für Chem., 1864, 629. And Russ. Zeitschr. für Pharm. III, 3, 49, 113, 121.

[10] E. Grimaux. Recherches synthetiques sur le groupe urique. Comptes rendus, 81, 325 (1875).

[11] H. Hill and C. Mabery. On the Ethers of Uric Acid. American Chem. Journ., 2, 305 (1880).

[12] Medicus. Zur Constitution der Harnsäuregruppe. Liebig's Ann. der Chem. u. Pharm., 175, 230 (1875).

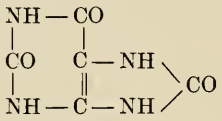
[13] J. Horbaczewski. Synthese der Harnsäure. Monatshefte für Chemie, 3, 796 (1882).

[14] *Ibid.* Ueber künstliche Harnsäure und Methylharnsäure. Monatshefte für Chemie, 6, 356 (1885).

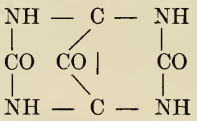
[15] R. Behrend und O. Roosen. Synthese der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 251, 235 (1889).

isodialuric acid. The latter combines with urea to form uric acid. The simplest method of synthesis, that of Fischer and Ach,[1] consists in withdrawing the elements of water from pseudouric acid with oxalic acid, or more easily with boiling concentrated hydrochloric acid.

In 1875 Medicus [2] proposed the formula



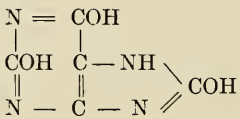
for uric acid, and in 1877 Fittig [3] proposed the formula



Emil Fischer, in 1882,[4] showed that the Medicus formula was probably the correct one, at any rate, that the Fittig formula could not be correct, since there exist two isomeric monomethyl uric acids. This, together with other evidence, showed Medicus' formula to be correct.

The formula proposed by Medicus agrees well with the chemical behavior of uric acid. From it we can understand the change to alloxan and urea and to carbon dioxide, ammonia, and glycocoll, the change to tetramethyl uric acid by the action of alkali and methyl iodide and finally the existence of isomeric mono-, di-, and tetramethyl uric acids.

The tautomeric formula



explains the acid properties and many of the reactions of uric acid.

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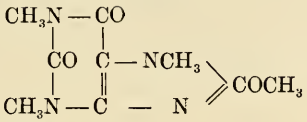
[1] E. Fischer und L. Ach. Neue Synthese der Harnsäure und ihre Methylderivate. Ber. der Dtsch. chem. Gesell., 28, 2473 (1895).

[2] Medicus. Zur Konstitution der Harnsäuregruppe. Liebig's Ann. der Chem. u. Pharm., 175, 230 (1875).

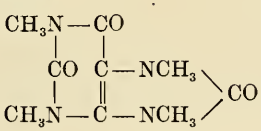
[3] R. Fittig. Wöhler's Grundriss der organischen Chemie. 10t Aufl., Leipzig, 1877, p. 309.

[4] E. Fischer. Umwandlung von Xanthin in Theobromin und Caffein. Ber. der Dtsch. chem. Gesell., 15, 395 (1882).

Both of these compounds may exist. It is impossible by our present methods to distinguish between these two formulæ, the lactam and the lactim. This same difficulty has appeared in determining the constitution of other bodies; for example, aceto-acetic acid, which sometimes appears to have the formula CH_3COCH_2COOH and sometimes $CH_3COHCHCOOH$. We know that the amorphous uric acid set free in the cold from salts has different properties from the crystalline uric acid obtained by boiling or on long standing. In the case of the alkyl derivatives we can, of course, easily tell whether or not the alkyl group is attached to nitrogen or oxygen. We have, in fact, derivatives of both the lactam and the lactim formula. Wislicenus and Kœrber [1] in changing methoxycaffein

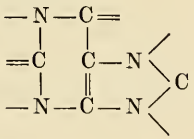


into tetramethyluric acid



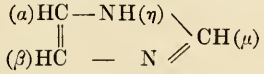
by heating have given us an example of change of one form into the other.

The C_5H_4 or, structurally,



group is called the purin nucleus by Emil Fischer, and all the purin bodies have both the meta-diazine and the imidazole rings.

Wallach [2] and Rung and Behrend [3] first showed that imidazol



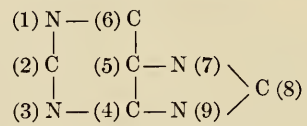
[1] Wislicenus und H. Kœrber. Ueber die Umlagerung von Laktimäthern in Laktame. Ber. der Dtsch. chem. Gesell., 35, 1991 (1902).

[2] Wallach. Ueber das Verhalten einige Diazo- und Diazoaminoverbindungen. Liebig's Ann. der Chem. u. Pharm., 235, 233 (1886).

[3] Rung und Behrend. Notizen über Glyoxalin. Liebig's Ann. der Chem. u. Pharm., 271, 28 (1892).

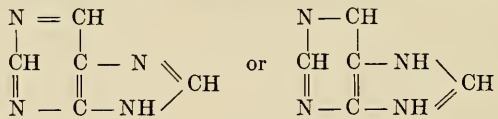
will react with diazo-bodies to form diazoamino compounds. They showed that imidazol will react with diazobenzolchlorid to form η-diazobenzolimidazol. Burian [1] showed that the α, β, and μ substitution products can also be diazotized, and that the action fails only when the hydrogen atom in position (η) is already substituted. This author showed that purin bodies like xanthin, hypoxanthin, guanin, adenin, and theophyllin (1, 3, dimethylxanthin), in which the hydrogen atom in position (7) is not substituted, can be made to form diazoamino compounds in the same way. In such compounds as caffein, 1, 3, 7, trimethylxanthin, and theobromin, 3, 7, dimethylxanthin, where the hydrogen atom in position (7) is substituted, no diazo derivative can be found. This is important as it gives us a method of finding how the purin bodies are combined in nucleic acids.

The Germans follow Fischer and number the atoms as follows:



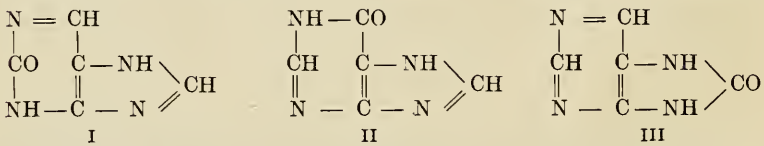
Some of the English follow a slightly different numbering.

We have the choice of two tautomeric formulæ for purin, viz.:



This tautomerism is observed in all derivatives of purin in which there is no oxygen in the imidazole ring, therefore in xanthin, hypoxanthin, adenin, theophyllin, etc., Emil Fischer has obtained in several cases both isomeric methyl products, where only one hydrogen compound exists.

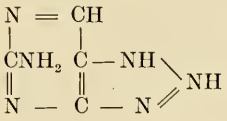
Theoretically, three monoxypurins are possible, I, II, and III.



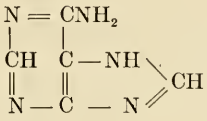
We can, of course, imagine the corresponding lactim formulæ

[1] R. Burian. Diazoaminoverbindungen der Imidazole und der Purinsubstanzen. Ber. der Dtsch. chem. Gesell., 37, 696 (1904).

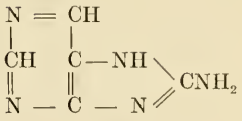
instead of the formulæ given. Formulæ II and III themselves and methyl derivatives are all three known. Similarly, there are three monoamino purins.



IV



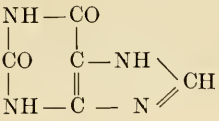
V



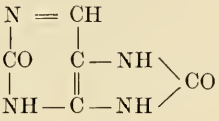
VI

V is adenin. Methyl derivatives of all three are known.

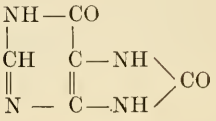
Three isomeric dioxypurins are likewise possible, VII, VIII, and IX.



VII



VIII



IX

VII, which is xanthin, and IX, and methyl derivatives of all three, have been prepared.

Synthetical Methods. — Five methods have been of especially great service in the synthesis of the members of the uric acid group by Fischer.[1]

1. The preparation of uric acid and its methyl derivatives from pseudouric acid.

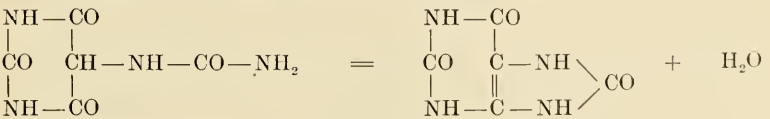
2. The methylating of uric acid and xanthin.

3. The change of uric acid and dioxypurin to chlor derivatives by the use of PCl_5.

4. The change from the chlor derivatives to the oxy, thio, and amino derivatives.

5. The reduction of the chlor purins with zinc dust or hydriodic acid.

Synthesis of Uric Acid from Pseudouric Acid. —



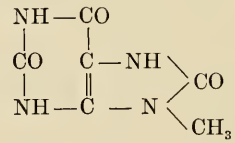
pseudouric acid — uric acid

[1] E. Fischer. Synthese in der Puringruppe. Ber. der Dtsch. chem. Gesell., 32, 435 (1899).

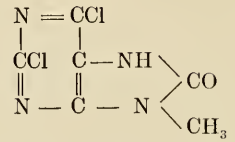
This dehydration was first brought about by melting pseudouric acid with oxalic acid.[1] Later, the simple method of boiling with hydrochloric acid was used.[2] This is only one of the many examples of synthesis by this method. It serves as a support for the formula we now hold for uric acid.

The Alkylating of the Oxypurins. — Hill and Mabery[3] first prepared methyl and dimethyl uric acid by heating lead urate with methyl iodide in a closed tube at 160°. Fischer's method of preparing methyl derivatives consists in shaking a solution of alkaline urate with warm methyl iodide. This method can be used with all oxypurins and their derivatives except the halogen derivatives. The latter react with more difficulty. Strecker[4] was the first to prepare a methyl xanthin.

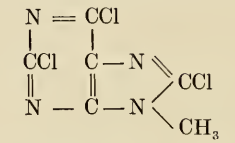
Preparation of the Chlor Purins. — E. Fischer first prepared chlor derivatives of purin by heating methyl uric acid



with phosphorus oxy-chloride and phosphorus pentachloride to 130°. He obtained 9-methyl-8-oxy-2-6-di-chlor-purin.



Further heating gave 9-methyl-tri-chlor-purin.



[1] E. Fischer und L. Ach. Neue Synthese der Harnsäure und ihrer Methylderivate. Ber. der Dtsch. chem. Gesell., 28, 2473 (1895).

[2] E. Fischer. Neue Synthese der Harnsäure, des Hydroxycaffeins und des Aminodioxypurines. Ber. der Dtsch. chem. Gesell., 30, 559 (1897).

[3] H. Hill and C. Mabery. On the Ethers of Uric Acid. American Chem. Journ., 2, 305 (1880).

H. Hill. Ueber die Æther der Harnsäure. Ber. der Dtsch. chem. Gesell., 9, 370 (1876).

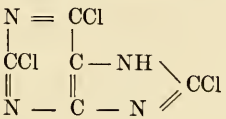
[4] A. Strecker. Untersuchungen über die chemischen Beziehungen zwischen Guanin, Xanthin, Theobromin, Caffein, und Kreatinin. Liebig's Ann. d. Chem. u. Pharm., 118, 151 (1861).

In obtaining chlorine derivatives in many of the group, the results depend in great measure on the temperature and the substituted radicles in the compound.[1]

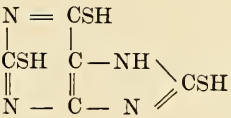
Change of the Halogen Purins into Oxy- Thio- and Amino-Purins. — The replacement of halogen by hydroxyl can be often brought about by aqueous alkali.[2] This method does not always work, however.[3] The output of hydroxycaffein, for example, by the action of aqueous alkali on chlor- or brom-caffein is small.[4] Much better results are obtained by the action of alcoholic alkali. Hydroxycaffein can be obtained in this way from chlor- or brom-caffein.[5]

Chlorine can be replaced by hydroxyl in almost all cases by the action of hydrochloric acid at 125°–130° C.[4,6]

The derivatives are prepared from the halogen derivatives by the action of KSH. For example, trichlorpurin



is changed to tri-thio-purin



by excess of KSH at 100°.[7]

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[1] E. Fischer. Ueber die Harnsäure. Ber. der Dtsch. chem. Gesell., 17, 328 (1884).

Ibid. Verwandlung des Theobromins in methylirte Harnsäuren. Ber. der Dtsch. chem. Gesell., 28, 2480 (1895).

Ibid. Ueber die Tetramethylharnsäure. Ber. der Dtsch. chem. Gesell., 30, 3010 (1897).

E. Fischer und L. Ach. Ueber das Oxydichlorpurin. Ber. der Dtsch. chem. Gesell., 30, 2208 (1897).

[2] E. Fischer. Ueber die beiden Methyltrichlorpurine. Ber. der Dtsch. chem. Gesell., 30, 1846 (1897).

[3] E. Fischer und L. Ach. Ueber die 1–9 Dimethylharnsäure und die 1–7–9 Trimethylharnsäure. Ber. der Dtsch. chem. Gesell., 32, 250 (1899).

[4] E. Fischer. Verwandlung des Theobromins in methylirte Harnsäuren. Ber. der Dtsch. chem. Gesell., 28, 2480 (1895).

[5] *Ibid.* Ueber Caffein, Theobromin, Xanthin, und Guanin. Liebig's Ann. der Chem. u. Pharm., 216, 253 (1882).

[6] E. Fischer und L. Ach. Ueber das Oxydichlorpurin. Ber. der Dtsch. chem. Gesell., 30, 2208 (1897).

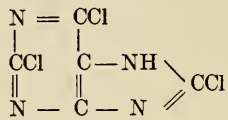
E. Fischer. Ueber die Tetramethylharnsäure. Ber. der Dtsch. chem. Gesell., 30, 3009 (1897).

E. Fischer und L. Ach. Ueber die 1–9 Dimethylharnsäure und die 1–7–9 Trimethylharnsäure. Ber. der Dtsch. chem. Gesell., 32, 250 (1899).

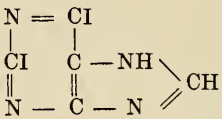
[7] E. Fischer. Ueber Thiopurine. Ber. der Dtsch. chem. Gesell., 31, 431 (1898).

Ammonia, alcoholic ammonia, and aqueous ammonia act on the chlor-purins and give amino derivatives. By the action of nitrous acid on the amino derivatives we can again obtain the oxypurins.

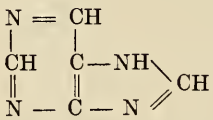
The Reduction of the Halogen Derivatives. — The halogen derivatives can be reduced to the hydrogen compounds by the action of HI or of phosphonium iodide.[1] In the case of the chlor-purins which do not contain oxygen, the action is more difficult.[2] If, however, we carry on the reaction at 0° C., iodo-purins are formed, and these can be reduced to the purins by the action of zinc dust and water.[3] Thus hydriodic acid changes trichlorpurin



to di-iodo purin



at 0°, and purin



is obtained from the latter by the action of zinc dust and water.

The Special Chemistry of the Important Purin Bodies and of the Monoureides

TRIOXYPURIN (URIC ACID) AND DERIVATIVES

Occurrence of Uric Acid. — Uric acid has been found in the urine of the elephant by Horbaczewski,[4] in the urine of swine

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[1] E. Fischer. Ueber die Harnsäure. Ber. der Dtsch. chem. Gesell., 17, 332 (1884).

[2] *Ibid.* Ueber Hydurinphosphorsäure. Ber. der Dtsch. chem. Gesell., 31, 2546 (1898).

[3] *Ibid.* Ueber das Purin und seine Methylderivate. Ber. der Dtsch. chem. Gesell., 31, 2550 (1898).

[4] Horbaczewski. Beiträge zur Kenntniss der Bildung der Harnsäure und der Xanthinbasen, sowie der Entstehung der Leucocytosen im Säugethierorganismus. Monatshefte für Chemie, 12, 221 (1891).

by Meissl and Strohmer,[1] Salomon,[2] and Mittelbach,[3] in camel's urine by Brand,[4] in horse's urine by Salkowski,[5] and Le Conte,[6] in cow's urine by Brücke[7] and Meissner and Shepard.[8] Mittelbach found it in the urine of all the herbivora that he studied, but not always in the urine of carnivora. It is often lacking in the urine of dogs and cats. According to Meissner,[9] it is found regularly only when they live on animal food or starve, and disappears when they live on food poor in proteid. Mills[10] found uric acid, but no urea, in the urine of the tortoise. Garrod[11] states that with the exception of the class of arachnids, scorpions and spiders for example, which excrete guanin, all the invertebrates excrete uric acid.

It was found in bladder stones and human urine by Scheele,[12] in gouty concretions by Pearson,[13] by Fourcroy and Vauquelin[14] in birds' excrement, and in serpent excrement by Prout.[15] It was not found in the urine of the carp, frogs, or sharks by Schreiber.[16] It was found in the green glands of the crab by Griffiths,[17] and in the malpighian vessels of periplaneta orientalis

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[1] E. Meissl und F. Strohmer. Ueber die Bildung von Fett aus Kohlenhydraten im Thierkörper. Monatshefte für Chemie, 4, 801 (1883).

[2] G. Salomon. Ueber die chemische Zusammensetzung des Schweinharn. Du Bois Arch. für Physiol., 8, 175 (1884).

[3] F. Mittelbach. Ueber das Vorkommen der Harnsäure im Harne der Herbivoren. Zeitschr. für physiol. Chem., 12, 465 (1888).

[4] G. Meissner. Ueber die Ausscheidung von Kreatin, Kreatinin, und einiger anderen stickstoffhaltigen Umsatzprodukten bei Säugethieren. Zeitschr. für ration. Med. (3), 31, 283 (1868).

[5] E. Salkowski. Zur Kenntniss des Pferdeharns. Zeitschr. f. physiol. Chem., 9, 241 (1885).

[6] Bernard. Leçons sur les liquides de l'organisme, 2, 59.

[7] E. Brücke. Harnsäure im Rindsharn. Jour. für prakt. Chem., 25, 254 (1842).
Ibid. Vorkommen von Harnsäure im Rinderharn. Müller's Arch., 1842, 91.

[8] Meissner und Shepard. Untersuchungen über das Entstehung der Hippursäure im Thierorganism, 81 (1866).

[9] G. Meissner. Ueber das Entstehen der Bernsteinsäure. Zeitschr. für ration. Med. (3), 24, 97 (1865).

[10] T. Mills. Notes on the Urine of the Tortoise, with Special Reference to Uric Acid and Urea. Journ. of Physiol., 7, 453 (1886).

[11] A. Garrod. Uric Acid: Its Physiology, and Its Relation to Renal Calculi and Gravel. Brit. Med. Journ., 495, 547, 601, 651, 704, and 751 (1883), I.

[12] K. W. Scheele. Examen chemicum Calculi urinarii. Opuscular, II, 73. Also, Lorenz Crell. Die neuesten Entdeckungen in der Chemie, III, 227.

[13] Pearson. Philosophical Transactions of the Royal Society, London, 1798, 15.

[14] Fourcroy et Vauquelin. Sur le guano ou sur l'engrais naturel des îlots de la mer du Sud près des côtes du Perou. Annales de Chimie, 56, 258 (1805).

[15] Thomson. Analysis of the Excrements of the Boa Constrictor. Annals of Philosophy, 5, 413.

[16] Schreiber. Ueber die Harnsäure unter physiologischen und pathologischen Bedingungen, 1899, 25. Stuttgart.

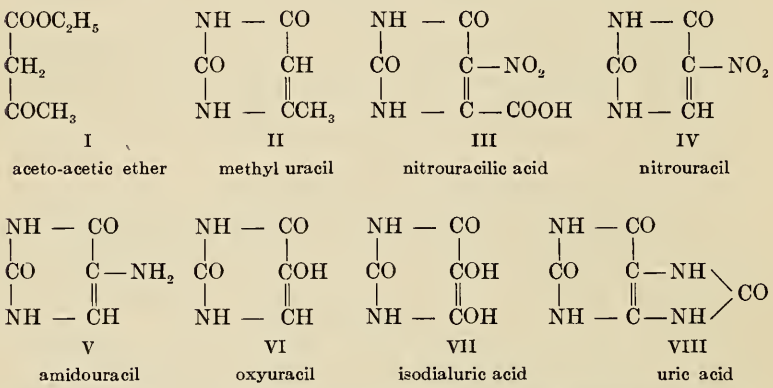
[17] A. Griffiths. On the Extraction of Uric Acid Crystals from the Green Gland of Astacus Fluviatilis. Chem. News, 51, 121 (1885).

by MacMunn.[1] Hopkins[2] found that the white pigment which lies between the two chitin layers of the scales of the pierida brassica is uric acid. Krukenberg[3] found uric acid in almost all the organs of lampyris splendidula, an invertebrate. Davy[4] found uric acid in the blood of invertebrates.

Synthesis of Uric Acid. — A study of the various syntheses of uric acid is of importance from a physiological standpoint, since, if uric acid is synthesized in the body, as some writers maintain, the synthesis may take place in a manner similar to one of the artificial methods.

Horbaczewski[5] was the first to synthesize uric acid. He gave two methods. The first consisted of fusing together glycocoll and urea, the second in fusing together the amide of trichloracetic acid and urea. The output in each case was small, and the methods have not been of general use in the synthesis of other members of the group.

Behrend and Roosen,[6] in 1888, synthesized uric acid from aceto-acetic acid and urea. The changes are shown below graphically:



[1] C. MacMunn. Note on a Method of Obtaining Uric Acid Crystals from the Malpighian Tubes of Insects and from the Nephridium of Pulmonate Molusca. Journ. of Physiol., 7, 128 (1886).

[2] F. Hopkins. The Pigments of the Pieridæ: A Contribution to the Study of Excretory Substances which Function in Ornament. Phil. Trans., London, 186, 661 (1895).

[3] Krukenberg. Vergl. Physiol. Studien an den Küsten der Adria, II. Abtheil, 29.

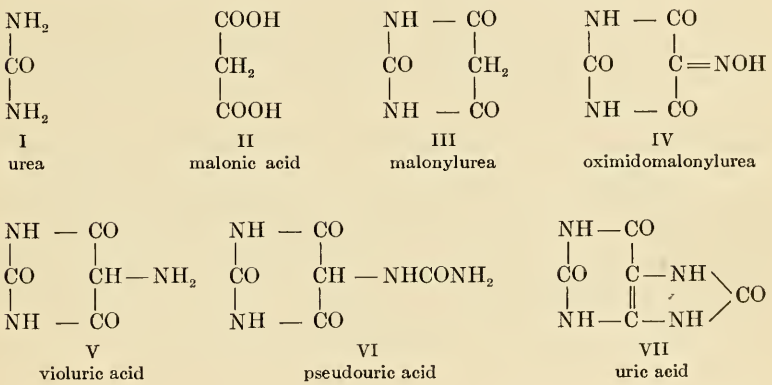
[4] A. Garrod. Uric Acid: Its Pathology and its Relation to Renal Calculi and Gravel. Brit. Med. Journ., 1883, I, 495, 547, 601, 651, 704, and 751.

[5] J. Horbaczewski. Synthese der Harnsäure. Monatshefte für Chemie, 3, 796 (1882).

[6] R. Behrend und O. Roosen. Synthese der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 251, 235 (1889).

β-ethyl-uramidocrotonic acid is obtained by heating together aceto-acetic acid (I) and urea. This, on treatment with KOH, gives methyl uracil (II). Concentrated nitric acid changes methyl uracil (II) to nitrouracilic acid (III), whose potassium salt on boiling gives nitrouracil (IV). Zinc and HCl reduce nitrouracil (IV) to amidouracil (V), and bromin changes amidouracil (V) to oxyuracil (VI) and isodialuric acid (VII). Under the influence of sulphuric acid isodialuric (VII) acid unites with urea to form uric acid (VIII).

Emil Fischer has given us a good general method for the synthesis of uric acid and its derivatives.[1] He treats pseudouric acid with oxalic acid or with hydrochloric acid. The complete synthesis from urea and malonic acid is given graphically below:



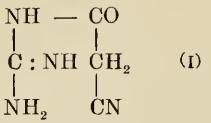
Urea (I) and malonic acid (II), when treated with $POCl_3$ give malonylurea (III). Nitrous acid changes malonylurea (III) to oximidomalonylurea (IV). Potassium cyanate (KCNO) and oximidomalonylurea (IV) react to form violuric acid (V), which unites with urea to form pseudouric acid (VI). Pseudouric acid changes to uric acid on treatment with hydrochloric or oxalic acid, which withdraws from the pseudouric acid the elements of water.

Traube [2] succeeded in synthesizing members of the purin group from cyanacetic ester ($CNCH_2COOC_2H_5$). This condenses with

[1] E. Fischer und L. Ach. Neue Synthese der Harnsäure und ihrer Methylderivate. Ber. der Dtsch. chem. Gesell., 28, 2473 (1895).

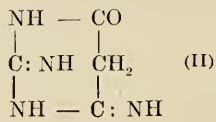
[2] W. Traube. Ueber eine neue Synthese des Guanins und Xanthins. Ber. der Dtsch. chem. Gesell., 33, 1371 (1900).

guanidin $NH : C(NH_2)_2$ in alcoholic solution to cyanacetylguanidin (I), which, under the influence of alkali, changes



(I)

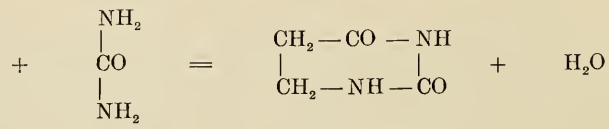
to iminomalonylguanidin or 2-4-diamino-6-oxypyrimidin (II)



(II)

The iminomalonylguanidin can be changed to guanin by the methods used to change pyrimidin derivatives to purin derivatives.[1] The guanin can then be changed to the other members of the purin group.

Another method for the synthesis of members of this group is that through the uracil derivatives. Emil Fischer[2] has given us the first part of the synthesis, — the preparation of uracil derivatives, a number of which he prepared and described. The uracils are prepared by union of β-amino acid esters and urea after withdrawal of the elements of water. Hydrouracil, for example, is prepared from acrylic acid and urea:



acrylic acid — urea — hydrouracil

The second part of the synthesis, the preparation of purins from uracils, is due to Gabriel and Coleman.[3] The synthesis of 6-2-methyl-amido-purin from methyl uracil is an example of their method.

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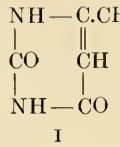
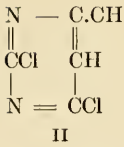
[1] S. Gabriel und J. Coleman. Synthesen in der Purinreihe. Ber. der Dtsch. chem. Gesell., 34, 1234 (1901).

[2] E. Fischer und G. Roeder. Synthese des Uracils, Thymins, und Phenyluracils. Ber. der Dtsch. chem. Gesell., 34, 3751 (1901).

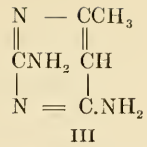
[3] Gabriel und Coleman. Synthesen in der Purinreihe. Ber. der Dtsch. chem. Gesell., 34, 1234 (1901).



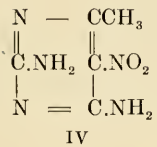
I



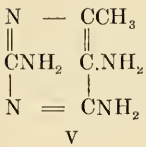
II



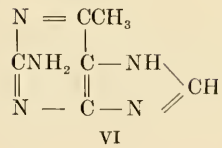
III



IV



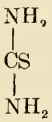
V



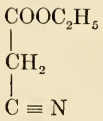
VI

PCl_5 changes methyl uracil (I) to di-chlor-methyl-pyrimidin (II), and this is changed to 4-2-6-diamido-methyl-pyrimidin (III) by ammonia. 4-2-6-diamido-methyl-pyrimidin (III) on nitration with concentrated nitric acid changes to 6-4-2-5-methyl-diamido-nitro-pyrimidin (IV), which, on reduction with tin and hydrochloric acid gives 6-4-2-5-methyl-tri-amido-pyrimidin (V). Formic acid changes the latter to 6-2-methyl-amido-purin (VI), which can, of course, be changed to uric acid and other members of the group.

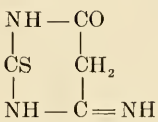
Still more recently Traube [1] has offered a new method of synthesizing purin derivatives from derivatives of urea and the monoureides. In the first method, thiourea



and cyanacetic ester

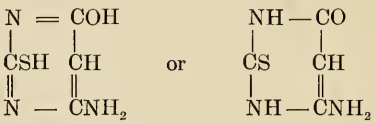


are condensed to form 4-amino-6-oxy-2-thio-pyrimidin,

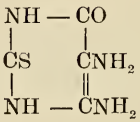


[1] W. Traube. Der Aufbau der Xanthinbasen aus der Cyanessigsäure. Synthese des Hypoxanthins und Adenins. Liebig's Ann. der Chem. u. Pharm., 331, 64 (1904).

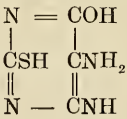
or 4-amino-2-thio-uracil,



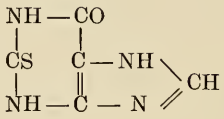
The methylene group of this compound reacts with nitrous acid with splitting off of H_2S to form an isonitroso compound which, on reduction, gives 4-5-diamino-2-thio-uracil,



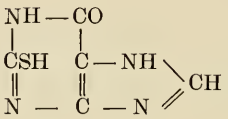
or 4-5-diamino-6-oxy-2-thio-pyrimidin,



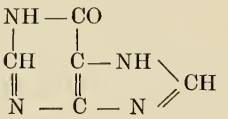
By heating the monoformyl derivative of this diaminothiouracil we get 6-oxy-2-thio-purin,



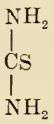
or 2-thiohypoxanthin,



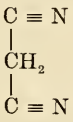
Nitric acid oxidizes this thiohypoxanthin to hypoxanthin,



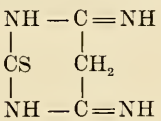
In the second method, thiourea,



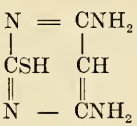
and malonitril (methyl cyanid),



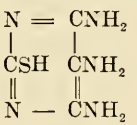
are condensed to 4-6-diamino-2-thio-pyrimidin,



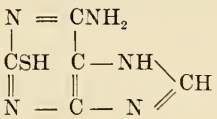
or 4-6-diamino-2-thio-uracil,



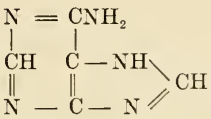
This is easily changed to the isonitroso derivative, and the latter reduced to 4-5-6-triamino-2-thio-pyrimidin,



If we boil this with formic acid, and heat the resulting compound, we get 2-thio-adenin, or 6-amino-2-thio-purin,

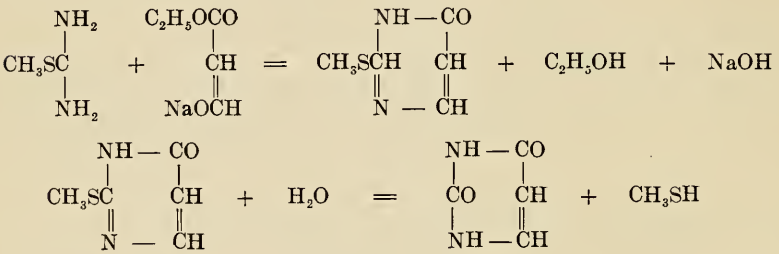


This changes to adenin,

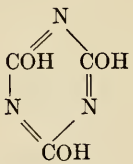


on treatment with hydrogen peroxide.

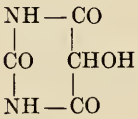
A synthesis of thymin has been proposed by Wheeler and Merriam.[1] Methyl-pseudo-thio-urea can be condensed with the sodium salt of formyl acetic acid to form a compound which, when boiled with concentrated HCl, gives thymin.



Decomposition and Oxidation of Uric Acid. — Uric acid decomposes on heating[2] into ammonia carbonic acid and cyanuric acid



If it is boiled with water for fifty hours with exclusion of air, dialuric acid



and urea are formed.[3]

According to Wöhler,[4] heating at 150° with water changes it to ammonium urate. No ammonia is formed by boiling it with the urates[5] or with magnesium[6] for four hours. According to

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[1] Wheeler and Merriam. On Some Condensation Products of the Pseudothioureas: Synthesis of Uracil, Thymin, and Similar Combinations. Am. Chem. Journ., 29, 478 (1903).

[2] K. W. Scheele. Examen chemicum Calculi urinarii. Opuscular II, 73. Also, Lorenz Crell. Die neuesten Entdeckungen in der Chemie, III, 227.

[3] M. Magnier de la Source. Action de l'eau sur l'acide urique. Bull. de la Soc. Chim. (2), 23, 483 (1875).

[4] Wöhler. Verfahren um Substanzen mit Wasser über 100° zu erhitzen. Liebig's Ann. der Chem. u. Pharm., 103, 118 (1857).

[5] Cazeneuve et Hugounenq. Sur un nouveau appareil pour le dosage precis de l'urée dans les liquides de l'organisme. Bull. de la Soc. Chim. (2), 48, 82 (1887).

[6] Berthelot et André. Contributions à l'histoire de la decomposition des amides par l'eau et les acides étendus. Bull. de la Soc. Chim. (2), 47, 840.

Kreidl,[1] a boiling solution of potassium urate begins to decompose after twelve hours, even in an atmosphere of nitrogen.

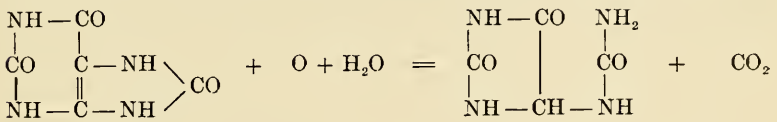
Gerard,[2] F. and L. Sestini,[3] and Kreidl [1] have shown that many micro-organisms decompose uric acid to urea. Ulpiana [4] and Cingolani [5] have recently isolated and prepared pure cultures of a micrococcus, which decomposes uric acid quantitatively into urea and CO_2 according to the reaction: $C_5H_4O_3N_4 + 2\,H_2O + 3O = 2\,CO(NH_2)_2 + 3\,CO_2$.

The decomposition of uric acid into glycocoll, carbon dioxide, and ammonia by the action of hydriodic or hydrochloric acid at 160°, first shown by Strecker,[6] is an important one.

Under the influence of the oxygen of the air, an alkaline solution of uric acid changes to uroxanic acid.[7,8] Reaction:

$$C_5H_4N_4O_3 + 2\,H_2O + O = C_5H_8N_4O_6.$$

In neutral or alkaline solution, such oxidizing agents as lead peroxide, manganese dioxide, potassium ferricyanide, cupric oxide, mercuric oxide, ozone, sodium and barium peroxide, potassium permanganate, or iodine, change uric acid to allantoin.[9]



uric acid — allantoin

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[1] J. Kreidl. Eine Bestimmungsmethode für Harnsäure und Beobachtungen an Harnsäurelösungen. Monatshefte. für Chemie, 14, 111 (1893).

[2] Gerard. Fermentation de l'acide urique par les microorganismes. Comptes rendus, 122, 1019 (1896) and 123, 185 (1896).

[3] F. and L. Sestini. Gaz. Chim. ital., 20, 133.

[4] C. Ulpiani. Ueber das Bakterium der Harnsäure. Atti R. Accad. dei Lincei. Roma (5), 12, II, 236; Gaz. Chim. ital., 33, II, 93, 1903, and Chem. Centralbl., 1903, II, 1287.

[5] M. Cingolani. Chemische Gleichung der Gärung der Harnsäure. Gaz. chim. ital., 33, II, 98, 1903; Chem. Centralbl., 1903, II, 1287.

[6] A. Strecker. Bildung von Glycocoll aus Harnsäure. Liebig's Ann. der Chem. u. Pharm., 146, 142 (1868).

[7] J. Kreidl. Eine Bestimmungsmethode für Harnsäure und Beobachtungen an Harnsäurelösungen. Monatshefte für Chemie, 14, 111 (1893).

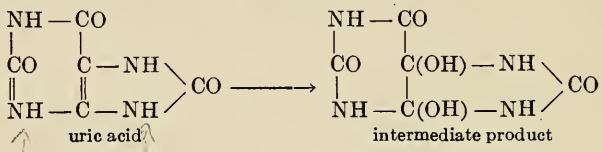
[8] Staedeler. Ueber die Uroxonsäure, ein Zersetzungsprodukt der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 78, 286 (1851).

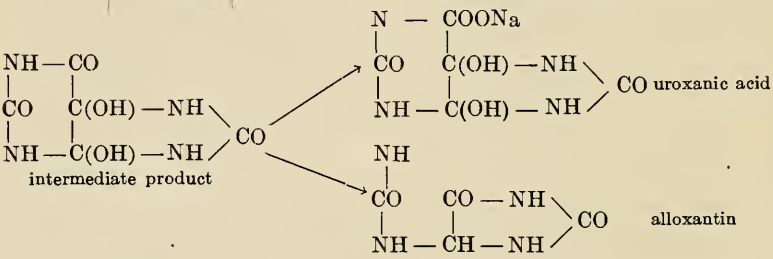
Nencki und Sieber. Ueber die Zersetzung des Traubenzuckers und der Harnsäure durch Alkalien bei der Bruttemperatur. Jour. für Prakt. Chem., 2 (24), 503 (1881).

v. Schröder. Beiträge zur Physiologie. C. Ludwig, 94 (1887).

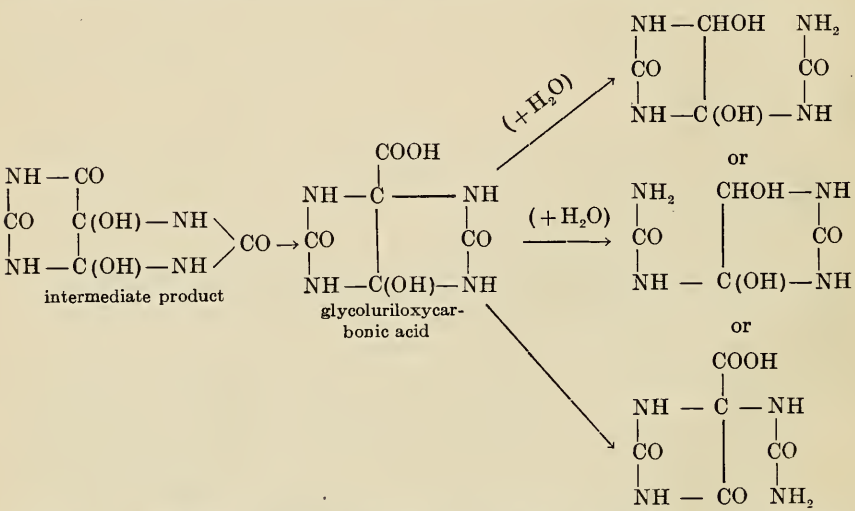
[9] W. Kruger. Eine neue Methode zur Bestimmung der Harnsäure im Harn. Zeitschr. für physiol. Chem., 21, 311 (1895). A. Claus. Zur Kenntniss der Harnsäuregruppe. Ber. der Dtsch. chem. Gesell., 7, 226 (1874). E. Bryk. Ueber die Einwirkung von Jod und Kalilauge auf Harnsäure. Monatshefte für Chemie, 15, 519, 1894.

According to Sundwik,[1] by the oxidation of uric acid in alkaline solution, we get first a certain compound, from which, by further oxidation, uroxanic acid is obtained when the solution is evaporated to dryness or allowed to stand, and from which allantoin is obtained if the alkali is neutralized, viz.,



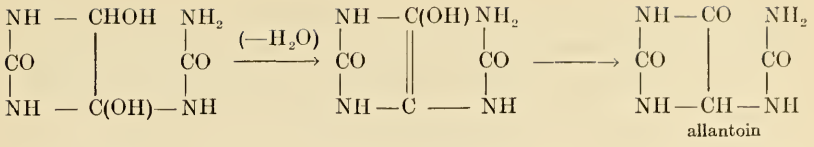


Behrend [2] believes, too, that this same intermediate product is formed and gives evidence that the further oxidation is as follows:



[1] E. Sundwik. Ueber die Bildung von Uroxansäure und Allantoin aus Harnsäure. Zeitschr. für physiol. Chem., 41, 343 (1904).

[2] R. Behrend. Ueber die Oxydation der Harnsäure in alkalischer Lösung. Liebig's Ann. der Chem. u. Pharm., 333, 141 (1904).



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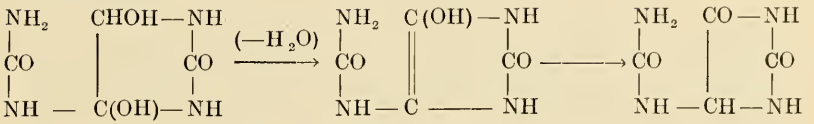

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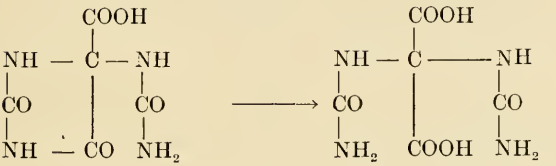
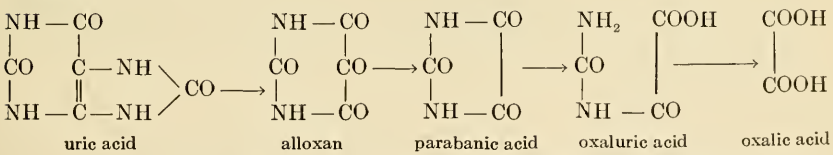


By gradual oxidation of uric acid in acid solution with cold concentrated nitric acid,[1] chlorine,[2] bromine,[3] or iodine,[2] manganese dioxide and sulphuric acid,[4] HCl and potassium chlorate,[5] or HIO_3,[6] we obtain first alloxan and urea. On heating, the alloxan oxidizes further to parabanic acid and carbon dioxide.[7] Alkalies change the parabanic acid to oxaluric acid,[1] which can be further decomposed to oxalic acid and urea by prolonged boiling with water. This series of changes is represented graphically below:



[1] Liebig und Wöhler. Untersuchungen über die Natur der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 26, 256 (1838).

[2] G. Brugnatelli. Sur un acide nouveau obtenu en traitant l'acide urique par l'acide nitrique. Annal. de Chim. et Phys., 8, 201 (1818).

[3] M. Hardy. Decomposition de l'acide urique par le brome, et l'action de la chaleur sur alloxan. Annal. de Chim. et Phys. (4), 2, 372.

[4] G. Wheeler. Notiz über die Einwirkung von Mangansuperoxyd auf Harnsäure. Zeitschr. für Chem., 746 (1866).

[5] Laurent, Gerhardt. Annal. de Chim. et Phys. (3), 24, 175.

[6] A. Archette. Einwirkung von Jodsäure auf Harnsäure. Boll. Chim. Farm., 43, 394 (1904), and Chem. Centralbl., 1904, 2, 318.

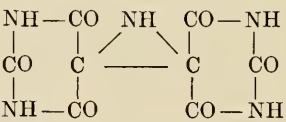
[7] Liebig und Wöhler. Verhalten des Alloxans beim Seiden mit Wasser. Liebig's Ann. der Chem. u. Pharm., 38, 357.

Fehling's solution[1] and alkali tungstate[2] likewise oxidize uric acid to oxalic acid and urea.

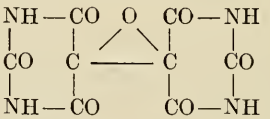
A new primary oxidation product of uric acid, tetracarbonimide,

has been obtained by Scholtz[3] by oxidation with hydrogen peroxide.

If to a warm solution of uric acid, nitric acid or chlorine water is added, and the solution evaporated to dryness, there remains a red residue which becomes purple red on addition of ammonia.[4] This is murexid, the ammonium salt of purpuric acid.

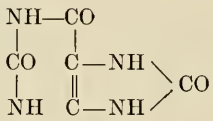


The nitric acid changes uric acid to alloxantin,

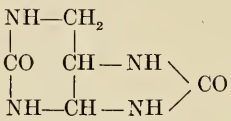


and ammonia changes the alloxantin to murexid.

Reduction of Uric Acid. — Emil Fischer did not succeed in reducing uric acid directly. He first chlorinated and then reduced the chlorine derivatives with hydriodic acid. Tafel,[5] in 1901, attempted to reduce the oxypurins in sulphuric acid solution by means of the electric current. He obtained, not purins but saturated bodies which he called purons. They were neither acids nor bases.



uric acid



puron

[1] Moritz. Ueber die Kupferoxydreducirenden Substanzen des Harns unter physiologischen und pathologischen Verhaltnissen. Archiv. für klin. Med., 46, 217 (1890).

[2] O. Maschke. Ueber das Verhalten der Wolframsäure zu einigen Bestandtheilen des Harns. Zeitschr. für anal. Chem., 16, 427 (1877).

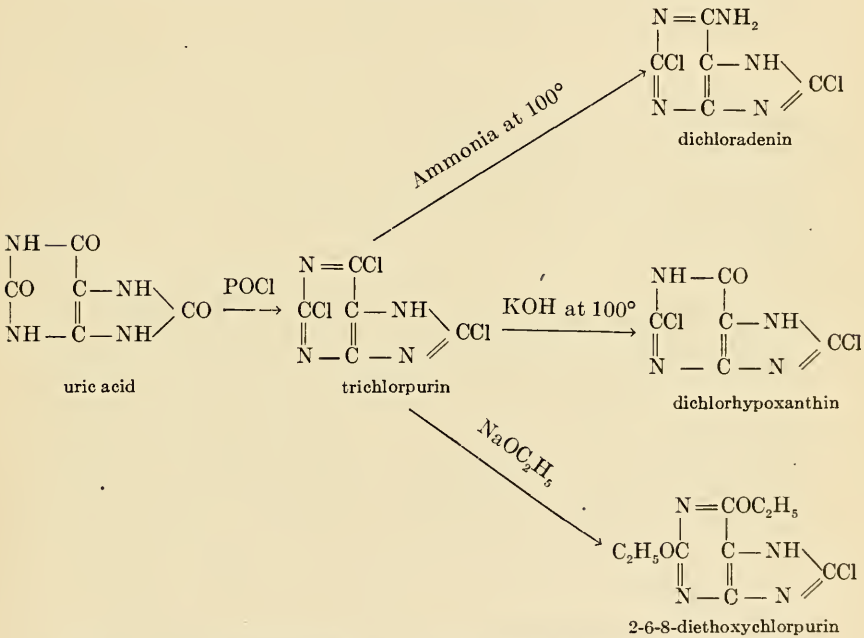
[3] M. Scholtz. Ueber ein neues Oxydationsprodukt der Harnsäure. Ber. der Dtsch. chem. Gesell., 34, 4130 (1901).

[4] Liebig und Wöhler. Untersuchungen über die Natur der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 26, 241 (1838).

[5] J. Tafel. Reduktionsprodukte der Harnsäure. Ber. der Dtsch. chem. Gesell., 34, 258 (1901).

He prepared and studied a number of bodies of this class. In another research [1] he found that the methyl derivatives of uric acid act in the same way and give methyl purons, a number of which he prepared and studied. Later, he studied the electrolytic reduction of xanthin,[2] guanin,[3] caffein,[4] and other purin derivatives.[5]

Relation of Uric Acid to Other Members of the Purin Group. — All the other members of the group can be derived from uric acid. The preparation of the principal members of the group from uric acid and their relations to it can be shown by the following scheme. The substance marked over the arrow in each case is what brings about the change.



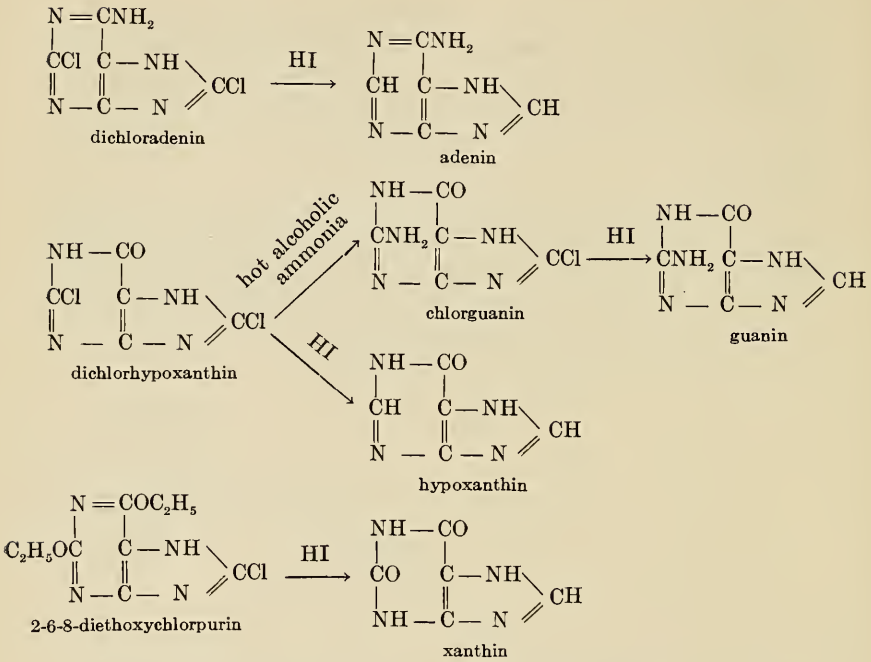
[1] Tafel. Reduktion Produkte aus methylirten Harnsäure. Ber. der Dtsch. chem. Gesell., 34, 279 (1901).

[2] J. Tafel und B. Ach. Elektrolytische Reduktion des Xanthins. Ber. der Dtsch. chem. Gesell., 34, 1165 (1901).

[3] Tafel und Ach. Reduktionsprodukte aus Guanin. Ber. der Dtsch. chem. Gesell., 34, 1170 (1901).

[4] J. Tafel und A. Weinschenk. Ueber 3-methyl-desoxyxanthin and desoxyheteroxanthin. Ber. der Dtsch. chem. Gesell., 33, 3369 (1900).

[5] J. Tafel. Ueber Desoxytheobromin. Ber. der Dtsch. chem. Gesell., 32, 3194 (1899).



Preparation of Uric Acid. — For the preparation of uric acid in large amounts, either snake excrement or guano is used. According to Bensch's [1] method, the uric acid is extracted with potassium hydrate and purified by precipitation with strong acid. In Strecker's [2] method, lime water is used for extraction, and the uric acid purified by a method similar to that of Bensch. Ludwig,[3] Salkowski,[4] Hopkins,[5] and Krüger and Wulff,[6] have given us methods of obtaining uric acid from human urine, and Knieriem,[7]

[1] A. Bensch. Ueber einiger Salze der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 54, 189 (1845).

[2] A. Strecker. Untersuchungen über die chemischen Beziehungen zwischen Guanin, Xanthin, Theobromin, Caffein, und Kreatinin. Liebig's Ann. der Chem. u. Pharm., 118, 151 (1861).

[3] E. Ludwig. Zur quantitativen Bestimmung der Harnsäure. Zeitschr. für anal. Chem., 21, 148 (1882). Wiener Med. Jahrbüch., 1884, 599.

Also, Ueber die Bestimmung der Harnsäure. Zeitschr. für anal. Chem., 24, 637 (1885).

[4] E. Salkowski. Weitere Beiträge zur Kenntniss der Leukämie. Virchow's Archiv, 52, 58 (1871).

[5] Hopkins. Bestimmung von Harnsäure im Harne. Chem. Centralbl., 1892, 2, 269.

[6] Krüger und Wulff. Ueber eine Methode zur quantitativen Bestimmung der sogenannten Xanthinkörper im Harne. Zeitschr. für physiol. Chem., 20, 176, 1895.

[7] W. Knieriem. Ueber das Verhalten der im Säugethierkörper als Vorstufen des Harnstoffs erkannten Verbindungen zum Organismus der Hühner. Ztsch. für Biol., 13, 36 (1877).

Meissner,[1] and Bensch [2] for the isolation of uric acid from bird's urine.

Qualitative Tests for Uric Acid. — If nitric acid or chlorine water is added to a solution of uric acid and the solution evaporated to dryness on the water bath, there remains a reddish residue which is changed to purple red with ammonia. Sodium hydroxide or potassium hydroxide will change this to reddish blue.[3] This is the murexid test, and is explained a few pages back. The presence of succinic or kynurenic acid spoils the test.[4]

If uric acid be warmed with a few drops of nitric acid, and then mixed in the cold with a few drops of the chlorhydrate of dimethyl-paraphenylendiamin in 1 or 2 per cent aqueous solution, there appears a purple red color, which, on warming and evaporating, changes to violet blue. This color disappears on cooling, but again reappears on warming.[5]

Another way of testing for uric acid is to warm the substance to be tested with nitric acid or bromine water until it boils, and then, after evaporation, to add two or three drops of concentrated sulphuric acid and a few drops of commercial benzene (containing thiophene). The presence of uric acid is shown by a blue color, which changes to brown on evaporation of the benzene, and again reappears on addition of the benzene.[6]

Confirmatory tests are the reduction of Fehling's solution and of silver nitrate by uric acid, and the formation of a blue color on treating a solution of uric acid with phospho-tungstic acid or phospho-molybdic acid.[7]

Quantitative Determination of Uric Acid. — The Ludwig-Salkowski [8] method is the one chiefly used. According to Warnecke,[9] Hopkins' method is not always accurate. This method

[1] Meissner. Beiträge zur Kenntniss des Stoffwechsels im thierischen Organismus. Zeitschr. für ration. Med. (3), 311, 144 (1868).

[2] A. Bensch. Ueber einige Salze der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 54, 189 (1845).

[3] Liebig und Wöhler. Untersuchungen über die Natur der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 26, 241 (1838).

[4] G. Meissner und C. Shepard. Untersuchungen über die Entstehung der Hippursäure im thierischen Organismus. Hannover, 1866, 113 und 203.

[5] P. Malerba. Un nuovo metodo per riconoscere l'acetone e l'acido urico. Atti della R. accad. med. e chir. di Napoli. Ao. XLVIII, Nuova Serie 2, from Maly's Jahresb. Ueber die Fortschritte der Thierchem., 24, 76 (1894).

[6] G. Denigès. Neue Reaction der Harnsäure. Jour. de Pharm. et de Chimie, 18, 161, 162.

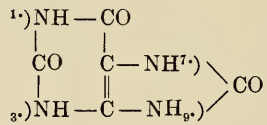
[7] See Huppert (Neubauer u. Vogel). Analyse des Harns, 3d ed., 1898, p. 331.

[8] *Ibid.* Analyse des Harns, 3d ed., p. 820.

[9] Warnecke. Ueber die quantitative Bestimmung der Harnsäure, etc. Dissert. Gottingen. (98).

depends upon the principle that uric acid in the presence of ammoniacal magnesia solution is precipitated as double salt by an ammoniacal silver solution. The uric acid is dissolved out of the double salt by alkali sulphide and then reprecipitated with hydrochloric acid. The technique of the method is found in the textbooks.[1] The methods of determining uric acid will not be discussed here.

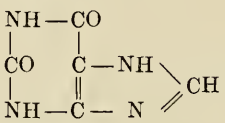
The Methyl Uric Acids. — Although the methyl uric acids themselves have not been shown to be of any physiological importance, they are of considerable importance in the study of the structure of uric acid.



According to this formula for uric acid we should expect four mono-methyl uric acids, the methyl groups being in positions 1, 3, 7, and 9 respectively. But, in fact, we have six mono-methyl uric acids.[2] The extra ones are called δ and ζ uric acid. Fischer and others have thought them to be stereo-isomers, but recently Fischer has stated that stereo-isomerism could not explain these extra-methyl uric acids. Behrend and Dietrich [3] thought δ-methyl uric acid was a 1-methyl uric acid, while E. Fischer [4] thought it a 3-methyl uric acid. Later, Behrend and Thurm [4] confirmed Fischer's view by a study of di-methyl-uracil obtained from δ-methyl uric acid.

DIOXYPURIN AND DERIVATIVES

Xanthin. — 2-6-dioxypurin.



[1] See Huppert (Neubauer u. Vogel). Analyse des Harns, 3d ed., 1898, p. 331.

[2] E. Fischer und L. Ach. Ueber die Isomerie der Methylharnsäuren. Sitzungsberichte der Königl. pr. Akad. Wiss. Berlin, 35, 633 (1899).

[3] R. Behrend und E. Dietrich. Ueber die Konstitution der δ-Methylharnsäure. Liebig's Ann. der Chem. u. Pharm., 309, 260 (1899).

[4] R. Behrend und R. Thurm. Ueber die Konstitution der Alkylderivate des Methyluracils und der δ-Methylharnsäure. Liebig's Ann., 323, 160 (1902).

In 1817, Marcet [1] found xanthin in bladder stones, and called it xanthic oxyd. Wöhler and Liebig studied its composition, and called it harnoxyd, on account of the fact that it contained one less atom of oxygen than uric acid. Its presence in muscle and pancreas was shown by Scherer.[2]

Strecker [3] and Scherer [4] first found xanthin in normal urine. Pecile [5] and Salomon [6] found it in the urine of swine, and Salomon [7] in dog's urine. Baginsky,[8] Stadthagen,[9] and Weiske,[10] have studied its occurrence in urine in disease.

The best practical method of obtaining xanthin is by the action of nitrous acid on guanin.[11]

Strecker [11] stated that xanthin can be prepared by the reduction of uric acid with sodium amalgam, but E. Fischer [12] could not confirm this.

The experimental proof that xanthin is a reduction product of uric acid is the synthesis of xanthin by E. Fischer.[13] Long before, he had shown its decomposition into alloxan and urea by

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[1] An Essay on the Chemical History and Medical Treatment of Calcal Disorders. London, 19 (1817).

[2] Scherer. Ueber Hypoxanthin, Xanthin, and Guanin im Thierkörper und den Reichthum der Pancreas-Drüse an Leucin. Liebig's Ann. der Chem. u. Pharm., 112, 257 (1859).

[3] A. Strecker. Ueber eine neue Base aus der Fleischflüssigkeit. Liebig's Ann. der Chem. u. Pharm., 102, 204 (1857).

Ueber das Sarkin. Liebig's Ann. der Chem. u. Pharm., 108, 129 (1858).

Ueber die Verwandlung des Guanins in Xanthin. Liebig's Ann. der Chem. u. Pharm., 108, 141 (1858).

[4] Scherer. Xanthicoxyd (Harnoxyd, härnige Säure), ein normaler Bestandtheil des thierischen Organismus. Liebig's Ann. der Chem. u. Pharm., 107, 314 (1858).

[5] D. Pecile. Guanin in Schweineharn. Liebig's Ann. der Chem. u. Pharm., 183, 141 (1876).

[6] G. Salomon. Ueber die chemische Zusammensetzung des Schweinharns. Du Bois Arch., 1884, 175.

Ibid. Virchow's Archiv, 95, 527.

[7] *Ibid.* Untersuchungen über die Xanthinkörper des Harns. Zeitschr. für physiol. Chem., 11, 413 (1887).

[8] A. Baginsky. Ueber das Verhalten von Xanthin, Hypoxanthin, und Guanin. Du Bois Arch., 1884, 176; also Ueber das Vorkommen von Xanthin, Guanin, und Hypoxanthin. Zeitschr. für physiol. Chem., 8, 397 (1884).

[9] M. Stadthagen. Ueber das Vorkommen der Harnsäure in verschiedenen thierischen Organen, ihr Verhalten bei Leukämie, und die Frage ihrer Entstehung aus der Stickstoffbasen. Virchow's Archiv, 109, 390 (1887).

[10] Weiske. Xanthin und Harnsäure im Harn eines kranken Schlafbockes. Zeitschr. für Biol., 11, 254 (1875).

[11] Strecker. Ueber einige Reduktionsprodukte des Allantoins und der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 131, 119 (1864).

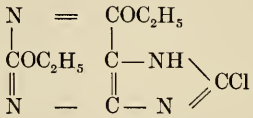
[12] E. Fischer. Ueber die Harnsäure. Ber. der Dtsch. chem. Gesell., 17, 328 (1884).

[13] *Ibid.* Synthese des Hypoxanthins, Xanthins, Adenins, und Guanins. Ber. der Dtsch. chem. Gesell., 30, 2226 (1897).

the action of Cl and HCl solution (analogous to the decomposition of uric acid) and its homology with theobromin and caffein.[1] The lead salt changes to theobromin (dimethylxanthin) on treatment with methyliodide.[1]

Xanthin can be synthetically prepared from uric acid in twc ways. In both methods trichlorpurin is first formed by the action of PCl_5 on uric acid.

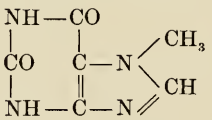
In the first method the trichlorpurin is changed to 2-6-dieth-oxy-8-chlor-purin



by the action of sodium ethylate (C_2H_5ONa), and this is changed to xanthin by the action of HI.[2] In the second method, the trichlorpurin is changed to diiodopurin by hydriodic acid at 0° and then to xanthin by HCl.[3]

These reactions prove the structure and the relation to uric acid. For the recognition of xanthin, its change to caffein, and, as analytical test also, its changes to brom-xanthin, brom-caffein, and ethoxy- and hydroxy-caffein are used.[3]

Heteroxanthin. — 7-methyl-xanthin.



Before Fischer's work the only monomethyl xanthin known was heteroxanthin. This was found in human urine by Salomon and Krüger.[4] Gottlieb and Bondzynski,[5] Albanese,[6] and Krüger and Salomon [4] have studied the amounts of heteroxanthin in the urine and tissues of man and other animals.

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[1] E. Fischer. Ueber Caffein, Theobromin, Xanthin, und Guanin. Liebig's Ann. der Chem. u. Pharm., 215, 253 (1882).

[2] *Ibid.* Synthese des Hypoxanthins, Xanthins, Adenins, und Guanins. Ber. der Dtsch. chem. Gesell., 30, 2226 (1897).

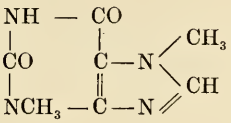
[3] *Ibid.* Ueber das Purin und seine Methylderivate. Ber. der Dtsch. chem. Gesell., 31, 2550 (1898).

[4] M. Krüger und G. Salomon. Die Konstitution des Heteroxanthins und seine physiologischen Wirkungen. Zeitschr. für physiol. Chem., 21, 169 (1895).

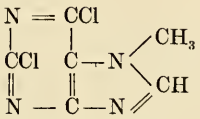
[5] Gottlieb und Bondzynski. Ueber Methylxanthin, ein Stoffwechselprodukt des Theobromins und Caffeins. Ber. der Dtsch. chem. Gesell., 28, 1113 (1895).

[6] M. Albanese. Ueber das Verhalten des Caffeins und des Theobromins im Organismus. Archiv. für exp. Path., 35, 449 (1895).

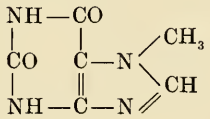
Krüger and Salomon proved its structure. They methylated it to caffein and changed it to sarkosin by the action of HCl. Fischer[1] has prepared it synthetically from theobromin. $POCl_3$ at 140° changes theobromin



to 7-methyl-2-6-dichlorpurin



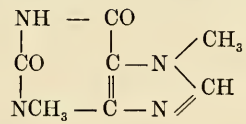
and this is changed to heteroxanthin



under the influence of HCl at 120°.

1-Methyl-Xanthin has been found in human urine by Krüger and Salomon,[2] and in the autolysis of the suprarenal capsule by Okerblom.[3] It has not yet been synthesized or its structure definitely proved.

Theobromin. — 3-7-dimethyl-2-6-dioxypurin



Theobromin is the most important dimethylxanthin. It was first found in cocoa beans by Woskresensky[4] in 1842. It is difficultly soluble in hot water or alcohol, but easily soluble in ammonia. It forms salts with acids. The silver salt gives caffein

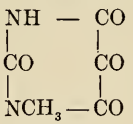
[1] E. Fischer. Ueber das Purin und seine Methylderivate. Ber. der Dtsch. chem. Gesell., 30, 2400 (1898).

[2] M. Krüger und G. Salomon. Die Alloxurbasen des Harnes. Zeitschr. für physiol. Chem., 24, 384 (1898).

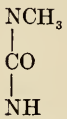
[3] J. Okerblom. Die Xanthinkörper der Nebennieren. Zeitschr. für physiol. Chem., 28, 60 (1899).

[4] Woskresensky. Ueber das Theobromin. Liebig's Ann. der Chem. u. Pharm., 41, 125 (1842).

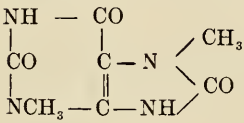
with methyl iodide.[1] Fischer [2] showed that it is dimethylxanthin and that chlorine changes it to monomethylalloxan



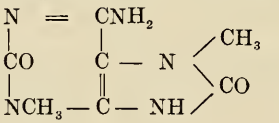
and monomethylurea.



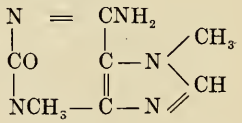
He was the first to synthesize it.[3] He treated 3-7-dimethyluric acid (I) with $POCl_3$ and PCl_5. The oxygen in position 6 is replaced by chlorine and then the chlorine is replaced by an amido group with ammonia. The structure of this 3-7-dimethyl-6-amino-2-8-dioxy-purin (II) follows from the fact that damp chlorine decomposes it to guanidin. By the action of $POCl_3$ the oxygen in position 8 is replaced by Cl. Reduction of this chloride changes it to 3-7-dimethyl-6-amino-2-oxy-purin (III)



I



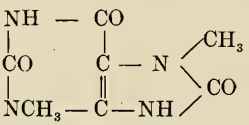
II



III

which is finally changed to theobromin by nitrous acid. The nitrous acid replaces the amino group by oxygen.

Two other simple syntheses of theobromin have been worked out by Ach and Fischer.[4] The first consists in changing 3-7-dimethyluric acid



[1] A. Strecker. Untersuchungen über die chemischen Beziehungen zwischen Guanin, Xanthin, Theobromin, Caffein, und Kreatinin. Liebig's Ann. der Chem. u. Pharm., 118, 151 (1861).

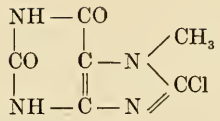
[2] E. Fischer. Umwandlung des Xanthins in Theobromin und Caffein. Ber. der Dtsch. chem. Gesell., 15, 453 (1882).

Ibid. Ueber Caffein, Theobromin, Xanthin, und Guanin. Liebig's Ann. der Chem. u. Pharm., 215, 253 (1882).

[3] *Ibid.* Synthese des Theobromins. Ber. der Dtsch. chem. Gesell., 30, 1839 (1897).

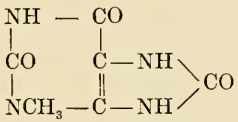
[4] E. Fischer und L. Ach. Weitere Synthesen von Xanthinderivaten aus methylirten Harnsäuren. Ber. der Dtsch. chem. Gesell., 31, 1980 (1898).

into chlortheobromin

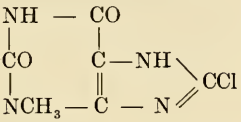


by boiling with $POCl_3$ and then replacing the chlorine by hydrogen in the usual way.

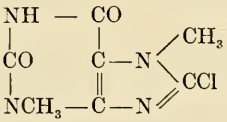
In the second method, 3-methyluric acid



is first changed to 3-methylchlorxanthin



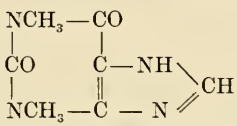
by the action of PCl_5, and then methylated to chlortheobromin



The chlorine compound is then reduced with hydriodic acid to theobromin.

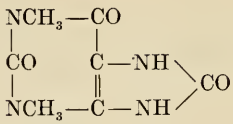
Since 3-methyl uric acid can be formed by direct methylating of the uric acid, we are now able to obtain theobromin directly from it. This method shows its structure and relation to uric acid.

Theophyllin. — 1-3-dimethyl-2-6-dioxypurin

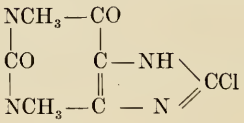


This was prepared by Ach and Fischer [1] by treating 1-3-dimethyluric acid

[1] E. Fischer und L. Ach. Synthese des Caffeins. Ber. der. Dtsch. chem. Gesell., 28, 3135 (1895).

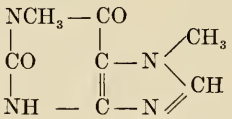


with $POCl_3$ and PCl_5. The chlor-theophyllin



thus formed was reduced to theophyllin by the action of hydriodic acid. This was the first derivative of xanthin synthetically prepared. It was discovered in tea in 1888 by Kossel.[1] He showed that it could be methylated to caffein and that damp chlorine changed it to dimethylalloxan.

Paraxanthin. — 1-7-dimethyl-2-6-dioxypurin.



Paraxanthin was found in urine by Thudicum in 1879,[2] and independently by Salomon,[3] who studied it chemically, and who, with Kruger [4] studied its occurrence in urine carefully. Emil Fischer synthesized it and proved its structure. It is changed to caffein by the action of hydriodic acid.[5] The position of the two methyl groups follows from Fischer's first synthesis from theobromin,[5]

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[1] A. Kossel. Ueber eine neue Base aus dem Pflanzenreich. Ber. der Dtsch. chem. Gesell., 21, 2164 (1888).

Ibid. Ueber das Theophyllin, einen neuen Bestandtheil des Thees. Zeitschr. für physiol. Chem., 13, 298 (1889).

[2] G. Thudicum. Untersuchungen über die Xanthinkörper des Harns. Zeitschr. für physiol. Chem., 11, 415 (1879).

[3] G. Salomon. Beiträge zur Chemie des Harns. Du Bois Archiv, 1882, 426.

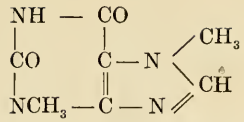
Ibid. Uber das Paraxanthin einen neuen Bestandtheil des normalen menschlichen Harns. Ber. der Dtsch. chem. Gesell., 16, 195 (1883).

Ibid. Ueber das Paraxanthin einen neuen Bestandtheil des normalen menschlichen Harns. Zeitschr. für klin. Med. 7, Suppl. Heft, 63 (1884).

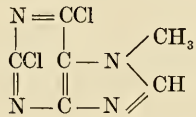
Ibid. Ueber Paraxanthin und Heteroxanthin. Ber. der Dtsch. chem. Gesell., 18, 3406 (1885).

[4] Krüger und Salomon. Die Konstitution des Heteroxanthins und seine physiologischen Wirkungen. Zeitschr. für physiol. Chem., 21, 169 (1895).

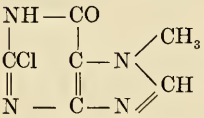
[5] E. Fischer Synthese des Heteroxanthins und Paraxanthins. Ber. der Dtsch. chem. Gesell., 30, 2409 (1897).



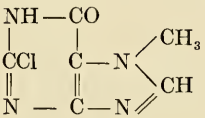
This is changed to 7-methyl-2-6-dichlorpurin



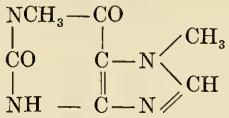
by the action of PCl_5, and then to 7-methyl-6-oxy-2-chlorpurin



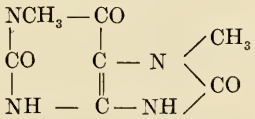
by replacing one of the chlorine atoms by hydroxyl with KOH. This is methylated to 1-methyl-2-chlor-6-oxy-7-methyl-purin



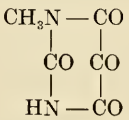
Chlorin is replaced by oxygen, giving paraxanthin.



By a second method of Fischer's,[1] 1-7-dimethyl uric acid

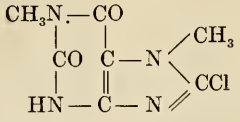


is obtained by condensation of urea and monomethyl-alloxan



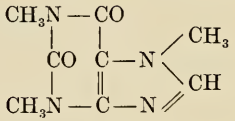
[1] E. Fischer und H. Clemm. Neue Synthese des Paraxanthins. Ber. der Dtsch. chem. Gesell., 31, 2622 (1898).

The dimethyl uric acid is changed to chlorparaxanthin



with phosphorus oxychloride, and this reduced to paraxanthin with hydriodic acid. Both methods prove the structure.

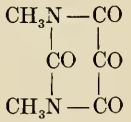
Caffein. — 1-3-7-trimethyl-2-6-dioxypurin.



Caffein was discovered in coffee in 1821 by Robiquet and Pelletier and Caventou.[1]

Oudry[2] found thein in tea, and Jobst[3] showed that caffein and thein are identical. Stenhouse[4] first showed that caffein is chemically related to the uric acid derivatives. By oxidation with HNO_3 he obtained a body similar to murexid, which Gerhardt showed to be dimethylparabanic acid. Rochleder[5] worked further with caffein and among other bodies found what he called amalinic acid, which Strecker[6] showed to be alloxantin.

E. Fischer[7] showed the decomposition by damp chlorine into dimethylalloxan



[1] Berzelius Jahresberichte, 4, 180, and 7, 269.

[2] Oudry. Thein, eine organische Salzbase im Thee. Mag. für Pharm., 19, 49 (1827).

[3] C. Jobst. Thein identisch mit Caffein. Liebig's Ann. der. Chem. u. Pharm., 25, 63 (1838).

[4] J. Stenhouse. Ueber Thein und seine Darstellung. Liebig's Ann. der Chem. u. Pharm., 45, 366 (1843).

Ibid. Nachträgliches über das Thein. Liebig's Ann. der Chem. u. Pharm., 46, 227 (1843).

[5] Rochleder. Ueber das Caffein. Liebig's Ann. der Chem. u. Pharm., 71, 1 (1849).

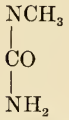
[6] A. Strecker. Untersuchungen über die chemischen Beziehungen zwischen Guanin, Xanthin, Theobromin, Caffein, und Kreatinin. Liebig's Ann. der Chem. u. Pharm., 118, 151 (1861).

[7] E. Fischer. Ueber das Caffein. Ber. der Dtsch. chem. Gesell., 14, 637 (1881).

Ibid., 14, 1905 (1881).

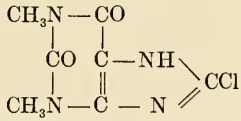
Ibid. Ueber Caffein, Theobromin, Xanthin, und Guanin. Liebig's Ann. der Chem. u. Pharm., 215, 253 (1882).

and monomethylurea

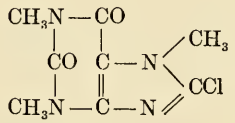


and thus proved the complete analogy to uric acid. He studied the chemistry of caffein much further and finally prepared it by methylating xanthin, and proved it to be trimethylxanthin, thus confirming the structure proposed by Medicus.

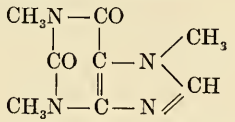
The first synthesis was that of Ach and Fischer.[1] 1-3-dimethyl uric acid is changed to chlortheophyllin



by the action of $POCl_3$ and PCl_5. The chlortheophyllin is methylated to chlorcaffein

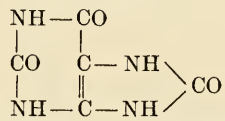


and the chlorcaffein reduced to caffein



by the action of hydriodic acid.[2] Since 1-3-dimethyl uric acid itself can be prepared from dimethylalloxan or dimethylmalonyl urea the complete synthesis is possible.

The second synthesis,[3] which was the first synthesis from uric acid itself, consisted in methylating uric acid



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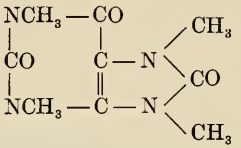
[1] E. Fischer und L. Ach. Synthese des Caffeins. Ber. der Dtsch. chem. Gesell., 28, 3135 (1895).

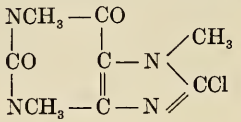
[2] E. Fischer. Ueber Caffein, Theobromin, Xanthin, und Guanin. Liebig's Ann. der Chem. u. Pharm., 215, 253 (1882).

Ibid. Ueber die Tetramethylharnsäure. Ber. der Dtsch. chem. Gesell., 30, 3009 (1897).

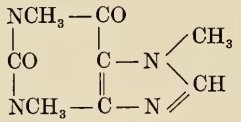
to tetramethyl uric acid



and then changing this by the action of PCl_5 to chlorcaffein

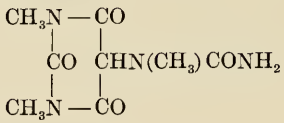


and finally reducing to caffein

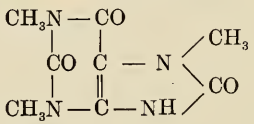


with hydriodic acid.

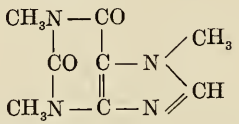
A third complete synthesis of Fischer's consists in heating 1-3-7-trimethylpseudo-uric acid



with HCl. This gives trimethyl uric acid

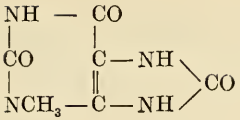


which can be changed to caffein

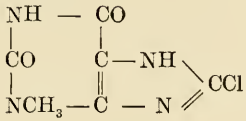


by chlorination and reduction.

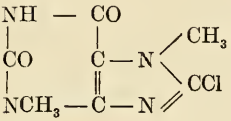
Two other syntheses which show the connection between caffein and uric acid have been worked out by Fischer and Ach. One leads from 3-methyl uric acid



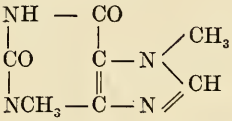
to 3-methyl-8-chlorxanthin



then to chlorcaffein

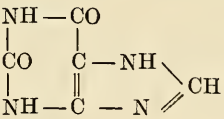


which is easily reduced to caffein.

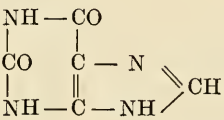


In the second, hydroxycaffein is obtained by direct methylation of uric acid in aqueous alkaline solution.[1]

The same tautomerism of the imidazol ring is present in xanthin as in purin, hypoxanthin, and adenin. We have derivatives of



and might expect some from



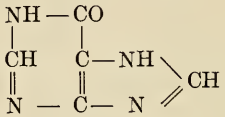
but none have as yet been prepared.

The other methyl derivatives of the dioxypurins are not of special physiological importance.

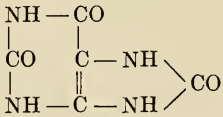
[1] E. Fischer. Synthese des Hypoxanthins, Xanthins, Adenins, and Guanins. Ber. der Dtsch. chem. Gesell., 30, 2226 (1897).

MONOXYPURINS AND DERIVATIVES

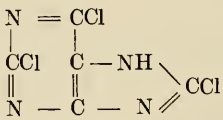
HYPOXANTHIN (sarkin). — 6 oxypurin.



Hypoxanthin is the only naturally occurring monoxypurin. It is found widely distributed in the animal body. It was found in urine by Salkowski [1] and Salomon [2] and Pouchet.[3] Thudicum,[4] Stadthagen,[5] and Baginsky [6] have studied the occurrence of hypoxanthin in disease. It was first prepared by Scherer in 1850.[7] Strecker,[8] Kossel,[9] and Krüger [10] have studied its structure, but this was finally determined by Fischer. He treated uric acid



with PCl_5 and obtained trichlorpurin.



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[1] E. Salkowski. Beiträge zur Kenntniss der Leukämie. Virchow's Archiv, 50, 174 (1870).

[2] Salomon. Beiträge zur Lehre von der Leukämie. Reichert's und Du Bois Archiv, 1876, 775. Also

Bieträge zur Chemie des Harns. Du Bois Archiv, 1882, 426. Also

Untersuchungen über die Xanthinkörper des Harns. Zeitschr. für physiol. Chem., 11, 410 (1887).

[3] Pouchet. Contributions à la connaisance des matières extractives de l'urine. Thèse, Paris, 1880.

[4] Thudicum. Grundzüge der anat. u. klin. Chim., 1886, 248.

[5] S. Stadthagen. Ueber das Vorkommen der Harnsäure in verschiedenen thierischen Organen, ihr Verhalten bei Leukämie, und die Frage ihrer Entstehung aus der Stickstoffbasen. Virchow's Archiv, 109, 390 (1887).

[6] A. Baginsky. Ueber das Vorkommen von Xanthin, Guanin, und Hypoxanthin. Zeitschr. für physiol. Chem., 8, 398.

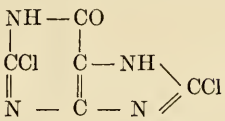
[7] Scherer. Ueber einen im thierischen Organismus vorkommen den dem Xanthicoxyd verwandten Körper. Liebig's Ann. der Chem. u. Pharm., 73, 328 (1850).

[8] A. Strecker. Ueber das Sarkin. Liebig's Ann. der Chem. u. Pharm., 108, 129 (1858).

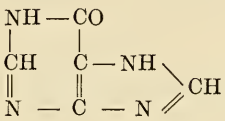
[9] A. Kossel. Ueber Xanthin und Hypoxanthin. Zeitschr. für phys. Chem., 6, 428 (1882).

[10] M. Krüger. Zur Kenntniss des Adenins und Hypoxanthins. Zeitschr. für physiol. Chem., 18, 445 (1894).

This changes to 6-oxy-2-8-dichlorpurin



by the action of aqueous alkali. Hydriodic acid changes this to hypoxanthin.[1]



Another way to obtain hypoxanthin from trichlorpurin is through adenin, 6-amino-purin. This changes to hypoxanthin on treatment with nitrous acid. For identification we can change it into the dimethyl derivative which has a characteristic melting point and compound with NaCl.

The methyl derivative of the monoxypurins are not of physiological importance.

AMINO-PURINS

Adenin. — This is the only important monoaminopurin. It is widely distributed in the animal kingdom. Adenin was found by Kossel,[2] and he and his pupils studied it, especially the well-known change to hypoxanthin on treatment with nitrous acid. HCl at 200° changes it to glycocoll, ammonia, and formic acid and carbon dioxide.[3] Bacteria, like nitrous acid, change adenin to hypoxanthin.[4]

Four formulæ are possible:

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[1] E. Fischer. Synthese des Hypoxanthins, Xanthins, Adenins, und Guanins. Ber. der Dtsch. chem. Gesell., 30, 2226 (1897).

[2] A. Kossel. Ueber eine neue Base aus dem Thierkörper. Ber. der Dtsch. chem. Gesell., 18, 79 (1885).

Ibid. Ueber das Adenin. Ber. der Dtsch. chem. Gesell., 18, 1928 (1885).

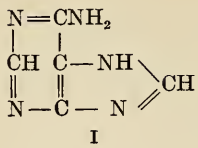
Ibid. Weitere Beiträge zur Chemie des Zellkerns. Zeitschr. für physiol. Chem., 10, 250 (1886).

Ibid. Ueber das Adenin. Zeitschr. für physiol. Chem., 12, 241 (1888).

[3] G. Bruhns. Ueber Adenin und Hypoxanthin. Ber. der Dtsch. chem. Gesell., 23, 225 (1890).

M. Krüger. Ueber die Konstitution des Hypoxanthins und des Adenins. Ber. der Dtsch. chem. Gesell., 26, 1914 (1893).

[4] S. Schindler. Beiträge zur Kenntniss des Adenins, Guanins, und ihrer Derivate. Zeitschr. für physiol. Chem., 13, 432 (1889).



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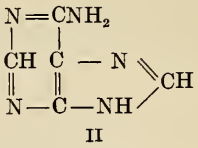

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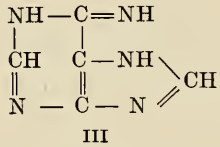
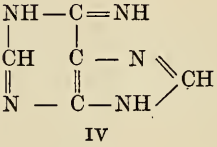


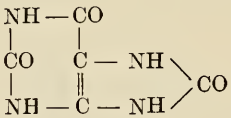
III



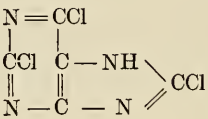
IV

Only two methyl derivatives of adenin are known. They have the methyl group in positions 7 and 9 respectively. From the indifference of these methyl compounds to alkalies, we can probably exclude formulæ III and IV, for the presence of the imido group in these purin bodies makes them soluble in alkali. Formula I is customarily used instead of Formula II.

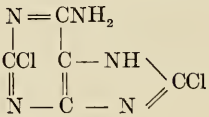
There are two ways of synthesizing adenin from uric acid. Uric acid



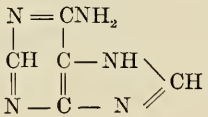
can be chlorinated to trichlorpurin



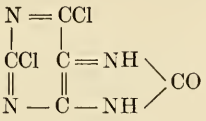
and the trichlorpurin changed to 6-amino-2-8-dichlorpurin



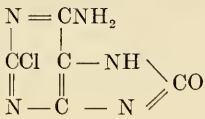
with ammonia, and finally reduced to adenin



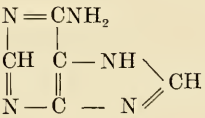
by means of hydriodic acid.[1] This method shows the position of the amino group. In the other synthesis, uric acid is changed to 8-oxy-2-6-dichlorpurin



by PCl_5, and this is changed to 6-amino-8-oxy-2-chlorpurin

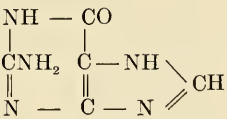


by ammonia. The last oxygen atom is replaced by chlorine and the product reduced with hydriodic acid to adenin.



The other amino purins and their methyl derivatives are not of physiological importance.

Guanin. — 2-amino-6-oxypurin



Guanin, the most important amino-oxypurin, was discovered by Unger [2] in guano. It was found in human urine by Pouchet,[3] especially in certain diseases, and by Pecile [4] in the urine of swine.

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[1] E. Fischer. Synthese des Hypoxanthins, Xanthins, Adenins, und Guanins. Ber. der Dtsch. chem. Gesell., 30, 2226 (1897).

[2] B. Unger. Ueber das Xanthin. Poggendorf's Ann. der Physik. u. Chemie, 65, 222 (1845).

Ibid. Bemerkungen zu einem Notiz über die Zusammensetzung des Harnoxyd von Embrodt. Liebig's Ann. der Chem. u. Pharm., 58, 20 (1846).

Ibid. Das Guanin und seine Verbindung. Liebig's Ann. der Chem. u. Pharm., 59, 58 (1846).

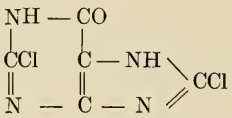
[3] Pouchet. Contributions à la connaisance des matières extractives de l'urine. Thèse, Paris, 1880, Parent, 28 u. 36.

[4] Pecile. Guanin im Schweineharn. Liebig's Ann. der Chem. u. Pharm., 183, 141 (1876).

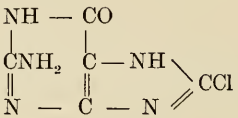
Salomon[1] and Baginsky[2] have also studied the occurrence of guanin in urine.

Virchow[3] and Mendelsohn[4] have reported cases where guanin nodules similar to the urate concretions found in human beings were found in hogs.

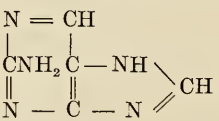
Guanin is found in the pancreas, and in tea, and is widely distributed in nature. It is insoluble in water, alcohol, and ether. Acids and bases act upon it, forming salts. Silver nitrate precipitates it from solution. Strecker[5] discovered and studied its change to xanthin on treatment with nitric acid, the change which shows its structure, and its change to guanidin on treatment with damp chlorine. It can be synthesized from 2-8-dichlorhypoxanthin.



This is treated with ammonia and changed to 2-amino-6-oxy-8-chlorpurin



and the latter reduced with hydriodic acid to guanin.



Bacteria, like nitrous acid, change guanin to xanthin.[6]

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[1] Salomon. Ueber die chemische Zusammensetzung des Schweinharns. Du Bois Arch., 1884, 175. Also Ueber die chemische Zusammensetzung des Schweinharns. Virchow's Archiv, 95, 527 (1884).

[2] Baginsky. Ueber das Vorkommen von Xanthin, Guanin, und Hypoxanthin. Zeitschr. für physiol. Chem., 8, 395.

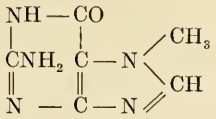
[3] Virchow. Ueber Konkretionen im Schweinfleisch welche naturscheinlich aus Guanin Bestehen. Virchow's Archiv, 35, 359 (1866).

[4] W. Mendelsohn. On Guanin Gout in the Hog, and its Relation to the Sodium Urate Gout of Man. Am. Journ. of Med. Sciences, New Series, 95, 109 (1888).

[5] Strecker. Ueber die Verwandlung des Guanins in Xanthin. Liebig's Ann. der Chem. u. Pharm., 108, 141 (1858).

[6] S. Schindler. Beiträge zur Kenntniss des Adenins, Guanins, und ihrer Derivate. Zeitschr. für physiol. Chem., 13, 432 (1889).

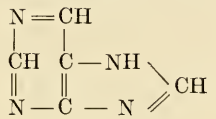
7-Methyl Guanin.—



This was found in urine by Krüger and Salomon[1] and is easily synthesized.[2] The same authors proved its identity with epiguanin.

The other amino-oxypurins, the thiopurins, and the halogen derivatives of the purins are not of special physiological significance.

PURIN

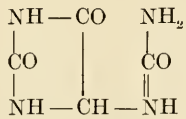


Purin itself was the most difficult of the group to prepare. It was finally obtained by Fischer in 1898.[3] He treated trichlorpurin at 0° C. with hydriodic acid, and obtained diodopurin, which was reduced with zinc dust. Purin is exceedingly soluble in water, and Fischer thinks that its great solubility may be the reason it has not been isolated from animals and plants.

THE MONOUREIDES

The purin derivatives on decomposition and oxidation give many of the different monoureides and their derivatives. It will be, perhaps, of some value to give a short sketch of the most important of these monoureides.

Allantoin



is a ureide of glyoxylic acid, that is glyoxylurea. It is an important oxidation product of uric acid from a physiological

[1] M. Krüger und G. Salomon. Epiguanin. Zeitschr. für physiol. Chem., 26, 389 (1898).

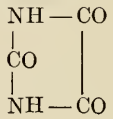
[2] E. Fischer. Synthese des Heteroxanthins und Paraxanthins. Ber. der Dtsch. chem. Gesell., 30, 2400 (1897).

Ibid. Ueber das Purin und seine Methylderivate. Ber. der Dtsch. chem. Gesell., 31, 2550 (1898).

standpoint. It was found by Prout[1] in the urine of new-born children, by Naunyn [2] in an ovarian cyst, by Gusserow [3] in the urine of men, by Pouchet[4] in human urine in pathological conditions sometimes in considerable amounts, by Moscatelli [5] in ascites fluid, and by Minkowski [6] and others in the urine of dogs and cats.

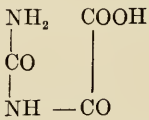
Its importance will be fully discussed later.

Parabanic acid, or oxalylurea,



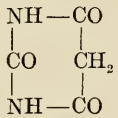
is obtained by oxidation of uric acid and alloxan by nitric acid.[7] It can be prepared synthetically by the action of $POCl_3$ on oxalic acid.[8]

Oxaluric acid



is formed by the action of alkali or of bromin on parabanic acid.[7] It is found in urine.[9]

Barbituric acid, or malonylurea,



is obtained by heating allantoin with H_2SO_4.[10]

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[1] Prout. Observations on the Nature of Some of the Principles of the Urine. Med. Chir. Trans., Vol. VIII, p. 526 (1818).

[2] Naunyn. Ueber die Chemie der Transudate und des Eiters. Arch. f. Anat. u. Physiol., 185 (1865).

[3] Gusserow. Zum. Lehre des Stoffwechsels des Fötus. Arch. f. Gynäkologie, III, 241 (1871).

[4] Pouchet. Contributions à la connaisance des matières extractives de l'urine. Thèse de Paris, 1880, 28.

[5] R. Moscatelli. Beiträge über den Zucker und Allantoin-Gehalt im Harn und in der Ascitesflussigkeit bei Lebercirrhose. Zeitschr. für physiol. Chem., 13, 202 (1889).

[6] Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

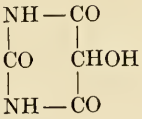
[7] F. Wöhler u. J. Liebig. Untersuchungen über die Natur der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 26, 241 (1838).

[8] M. Grimaux. Recherches synthetique sur la serie urique. Ann. de Chim. et de Physique, (5) 11, 356 (1877).

[9] Schlunk. Jahresberichte über die Fortschritte der Chemie, 1866, 749.

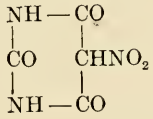
[10] Finck. Zersetzungsprodukte des Thioursäurem Ammoniaks. Ann. der Chem. u. Pharm., 132, 298 (1864).

Dialuric acid, or tartronlyurea,



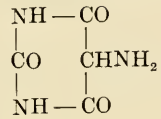
is obtained by reducing alloxan with zinc and HCl.[1]

Dilituric acid, or nitromalonylurea,



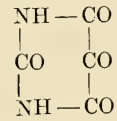
is otained by nitration of barbituric acid with concentrated nitric acid.[2]

Uramil, murexan, or amidomalonylurea,



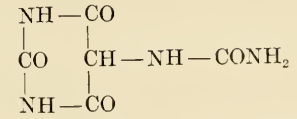
is obtained by reduction of dilituric acid with hydriodic acid.[3] It can be oxidized to alloxan by nitric acid.

Alloxan, or mesoxalylurea,



is obtained by moderate oxidation of uric acid or alloxantin.[1]

Pseudo-uric acid



is used in the synthesis of uric acid. Its ammonium salt can be obtained from uramil and urea.[4]

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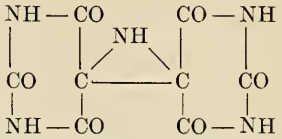
[1] Liebig und Wöhler. Untersuchungen über die Natur der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 26, 241 (1838).

[2] Bæyer. Untersuchungen über die Harnsäuregruppe. Liebig's Ann. der Chem. u. Pharm., 130, 129 (1864).

[3] *Ibid.* 127, 199 (1863).

[4] E. Gremaux. Sur l'acide pseudo-urique. Bull. de la Soc. Chim., 31, 535 (1879).

Purpuric acid,



The ammonium purpurate is the murexid obtained in the murexid test.

Uric Acid and Urates in Solution

Minkowski [1] says that in the treatment of gout especial attention has been directed to four points:

First — Decreasing the formation of uric acid.

Second — Hastening its excretion.

Third — Hastening its oxidation.

Fourth — Increasing its solubility in the blood and in the tissues.

After considering briefly the first three points, he says in speaking of the fourth, that the greatest value in the treatment of gout has, in general, been laid on methods of increasing the solubility of uric acid. The fact that uric acid is stored up in gouty concretions in the form of a difficultly soluble compound has led to attempts to get rid of it by making the solubility conditions more favorable.

It is, then, of the greatest importance that the solubility of uric acid and its important salts in pure water, in blood serum, and in urine should be known, and that the effect of different acids, salts, bases, and organic compounds on the solubility should be understood. There is a great deal of misapprehension on this subject, and therapeutics and treatment based on an inaccurate and false knowledge of the solubility relations of uric acid should be corrected.

Aqueous Solutions of Uric Acid and the Urates

URIC ACID

In Pure Water. — The values given in the literature for the solubility of uric acid in pure water have varied considerably.

Prout and Mitscherlich found that one part of uric acid dissolves in 10,000 parts of water. Henry found that it dissolves

[1] O. Minkowski. In Von Leyden's Handbuch der Ernährungstherapie, Vol. II, p. 510. Leipzig, 1898.

in 1,720 parts of cold, and 1,400 parts of boiling water, and in 1,000 parts of urine.[1]

The solubility as determined by Bensch[2] was the value held for a long time. His results give the solubility of uric acid as one part in 14,800 to 15,300 cold water, and one part in 1,800 to 1,900 of hot water. For the determination in cold water, he boiled water containing an excess of uric acid, then cooled the solution for eight days, and after filtering off the excess of uric acid, evaporated a measured volume of the solution to dryness. Behrend and Roosen[3] used the same method as Bensch, and found the solubility of uric acid one part in 10,000 of water at 18.5°.

In 1875, Magnier de la Source[4] showed that water decomposes uric acid and that the result obtained for the solubility of the acid by saturating at a high temperature and then cooling was a function not only of the final temperature, but of the maximum temperature and of the length of time the acid has stood in contact with the water. According to him, the following two reactions take place:

$$\underset{\text{uric acid}}{C_5H_4N_4O_3} + 2H_2O = \underset{\text{urea}}{CO(NH_2)_2} + \underset{\text{dialuric acid}}{C_4H_4N_2O_4}$$

and

$$\underset{\text{uric acid}}{C_5H_4N_4O_3} + 2H_2O + O = \underset{\text{uroxanic acid}}{C_5H_8N_4O_6}$$

Gigli[5] has shown that uric acid can change completely to urea by the action of water at the ordinary temperature after a number of months.

Blarez and Deniger[6] found that if the solutions were saturated at 100° and then cooled to the temperature at which the solubility was to be determined they obtained varying results, dependent upon the time during which the solution was kept at 100°, and likewise upon the time of cooling. If they saturated at the re-

[1] W. Henry. De acido urico et morbis a minia ejus secretione ortis. Edinburgh, 1807. Berzelius. Lehrbuch der Chemie. Wöhler's German Translation, 3d ed., 184, Vol. IX, p. 409.

[2] Bensch. Ueber einige Salze der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 54, 189 (1845).

[3] Behrend und Roosen. Synthese der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 251, 235 (1889).

[4] Magnier de la Source. Action de l'eau sur l'acide urique. Bull. de Soc. Chim., 23, 483 (1875).

[5] T. Gigli. Ueber die spontane Umwandlung der Harnsäure in Harnstoff. Chem. Zeitung, 25, 741.

[6] Blarez et Deniger. Solubilité de l'acide urique dans l'eau. Comptes rendus, 104, 1847 (1887).

quired temperature, their results were more constant. They likewise found that the water became saturated in a short time if it were well shaken. The amount of uric acid in the solution was determined by titrating the solution with potassium permanganate. The solubility of uric acid, according to them, is one part in 16,700 at 20° C.

All the determinations made previous to 1887 are then incorrect, on account of the decomposition of the uric acid by boiling.

According to Camerer,[1] uric acid is soluble in 14,000 parts of water at 15° C., 7,000 to 8,000 parts of water at 37° C., and of 2,000 parts of boiling water.

Bunge[2] confirmed the results of Camerer for the body temperature, but did not give his method of determination.

Smale[3] found one part uric acid soluble in 2,400 parts of water at 40° C. He shook an excess of the acid with water at 40° and weighed the undissolved residue.

Nicolais[4] shook an excess of uric acid with water at 18° and at 37°, and weighed the undissolved residue. He found the solubility to be one part in 16,300 of water at 18° and one part in 13,900 of water at 37°.

Huppert[5] gives the solubility of uric acid as one part in 16,000 of cold water, one part in 1,600 of hot water.

His and Paul[6] first called attention to the fact that since the solubility of uric acid is so small, the determination in the ordinary way would probably not be correct. The solubility of difficultly soluble substances is greatly affected by the presence of impurities in solution. They showed that the impurities found in ordinary distilled water very considerably change the solubility of uric acid.

In their determinations they took particular pains to get rid of all possible sources of error. They used especially pure uric acid and pure water prepared with especial precautions. The purity of the water was attested by its very low electrical con-

[1] Camerer. Zur Lehre von der Harnsäure und Gicht. Deutsche Med. Wochenschrift, 17, 10, 356 (1891).

[2] Bunge. Lehrbuch der physiol. u. pathol. Chem., 4th ed.

[3] Smale. Beiträge zur Kenntniss der Lösungsbedingungen der Harsäure im Harn. Centralbl. für Physiol., 385 (1895).

[4] Nicolais. Experimentelle und Klinischesü ber Urotropin. Zeitschr. für klin. Med., Bd. 37, 366 (1899).

[5] Neubauer und Vogel. Analyse des Harns, 3t ed., Wiesbaden, 188, p. 314.

[6] His und Paul. Physikalisch-chemische Untersuchungen über das Verhalten der Harnsäure und ihre Salze in Lösungen. Zeitschr. für physiol. Chem., 31, 1 (1900).

ductivity ($0.8 - 1.0 \times 10^{-6}$). The vessels used were very resistant to the action of water, on account of the fact that distilled water attacks ordinary glass and dissolves some of the constituents of the glass.

The uric acid was dissolved by shaking with water at the temperature at which a determination of the solubility was desired, and was left as short a time as possible in contact with the water after saturation. The solubility was determined by weighing the undissolved residue. The electrical conductivity of water purified by distillation in the ordinary way was found to be about half that of a saturated solution of uric acid. This high relative conductivity indicates that the amount of ammonia, carbonic acid, and alkaline silicates and carbonates to which it is due is enough to considerably influence the solubility of the uric acid. They found the solubility to be one part in 39,480. The dissociation into hydrogen ions and negative uric acid ions is about 95 per cent in a saturated solution.

The Effect of Acids on the Solubility of Uric Acid. — We find many statements in the literature to the effect that uric acid is more soluble in strong mineral acids,[1] H_2SO_4 and HCl, than in pure water. We do not find this statement in the books of Liebig, Poggendorf, and Wöhler, Berzelius-Wöhler, Beilstein, Bunge, Neumeister, and Hoppe-Seyler. Zabelin[2] says that HCl has no influence on the solubility of uric acid.

Xanthin, guanin, and theobromin are amphioteric electrolytes; that is, they can act as bases and form salts with acids, or they can act as acids and form salts with bases. A saturated solution of theobromin is dissociated to the extent of 0.27 per cent into positive hydrogen ions and negative theobromin ions.[3] The dissociation into positive theobromin ions and negative hydroxyl ions is only one millionth of its dissociation into negative theobromin ions and positive hydrogen ions, or about one ten-

[1] Fehling Handwörterbuch der Chemie, 1878, Vol. III, p. 584. Ladenburg Handwörterbuch, 1893, Vol. V, p. 7.

Rudel. Zur Kenntniss der Lösungsbedingungen der Harnsäure in Harn. Arch. für exp. Path. u. Pharmak., 30, 469 (1892).

Smale. Beiträge zur Kenntniss der Lösungsbedingungen der Harnsäure in Harn. Centralbl. für Physiol., 9, 385 (1895).

Hammarsten. Lehrbuch der physiologischen Chemie. 4t Auflage, 1899, p. 44.

[2] Zabelin. Ueber die quantitative Bestimmung der Harnsäure im Harn mittelst Salzsäure. Liebig's Ann. Suppl., 2, p. 313 (1863).

[3] T. Paul. Untersuchungen über Theobromin und Koffeïn und ihre Salzbildung. Arch. der Pharm., 239, 48.

thousandth to one forty-thousandth the basic dissociation of anilin.[1] Theobromin, then, is more soluble in either acid or alkali than in pure water.

From the analogy in chemical constitution between uric acid, theobromin, xanthin, and so forth, it had been thought that uric acid would form salts with acids and thus be more soluble in them than in pure water. This question, of course, has a practical interest, since uric acid is sometimes determined by precipitating from its salts with acids, and, further, we must first know the effect of acid on its solubility in pure water before we can arrive at any conclusions regarding the solubility of uric acid in physiological fluids.

A priori we should expect that if uric acid does not form salts with acids, that is to say, if it has acid but not basic properties, it would be less soluble in acids than in pure water. All acids are dissociated in solution to a greater or less extent into the positive ion or cation, hydrogen, and the negative ion or anion, which is composed of the rest of the molecule. Uric acid, $C_5H_4N_4O_3$, as His has shown,[2] is about 10 per cent dissociated (in saturated solution) into the positive hydrogen ion and the negative ion $C_5H_3N_4O_3$. We know that the concentration of the anion and the cation are determined by the equation

$$\frac{P \times N}{U} = K$$

where P stands for the concentration of the positive ion and N for the concentration of the negative ion, and U for the undissociated part of the acid. K is a constant for any given temperature and concentration of acid. In the case of a saturated solution, U becomes a constant equal to the solubility constant of the acid, and the equation becomes $P \times N = KU = K_1$. If a dilute mineral acid, for example HCl, is added to the solution, P increases very considerably, for mineral acids are almost completely dissociated at moderate dilution. If P increases, N must decrease in order that $P \times N$ remain constant. That is, the

[1] T. Paul. Untersuchungen über Theobromin und Koffeïn und ihre Salzbildung. Arch. der Pharm., 239, 48.

[2] W. His und T. Paul. Physikalisch-chemische Untersuchungen über das Verhalten der Harnsäure und ihrer Salze in Lösungen. Zeitschr. für physiol. Chem., 31, 1 (1900).

amount of dissociated uric acid must decrease, and, since the solubility of the undissociated part is a constant, a decrease in the undissociated part means a decrease in the solubility of the acid. In other words, acids should decrease the solubility of uric acid in water.

From theoretical considerations, His[1] came to the conclusion that solutions of strong mineral acids in concentrations of from about normal down to one one-hundredth normal would dissolve uric acid to the extent of about one part in 43,600 of solution. He showed by experiment that his calculations were correct. He concluded that the uric acid in salts in aqueous solution can be determined by precipitation with HCl, if certain precautions are taken. A correction of 2 mg. must be made for each 100 cc. of solution at 18° C. Klemperer[2] found that the presence of considerable carbonic acid decreases the solubility of uric acid. This is what we should expect from theoretical reasons.

With concentrated sulphuric acid, uric acid forms a crystalline salt.[3] This is decomposed by water, and does not, therefore, exist in aqueous solution.

If the concentration of the hydroxyl ions in a solution is increased, its solvent action for uric acid is increased. In a saturated solution of uric acid, the equation $H \times N = KU$ determines the equilibrium, where H is the concentration of the hydrogen ions, N the concentration of the negative uric acid ions, and KU a constant. Free hydrogen ions and free hydroxyl ions cannot exist together in a solution to more than a slight extent. Undissociated water is immediately formed. As fast as hydrogen ions disappear by union with hydroxyl ions, more undissociated uric acid is formed in order that $H \times N$ should remain constant, and more undissolved uric acid goes into solution. Addition of any caustic alkali causes increase in the concentration of hydroxyl ions, for alkalies are dissociated into the positive metallic ion and the negative hydroxyl ion. This is the cause of the increased solubility of uric acid in alkalies.

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[1] His und Paul. Physikalisch-chemische Untersuchungen über das Verhalten der Harnsäure und ihrer Salze in Lösungen. Zeitschr. für physiol. Chem., 31, 64 (1900).

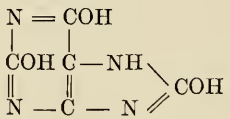
[2] G. Klemperer. Beiträge zur Erklarung harnsäurer Niederschläge in Urin. Zeitschr. für physik. und diät. Therapie, 5, 48 (1901–2).

[3] Fritzsch. Verbindung von Harnsäure mit Schwefelsäure. Liebig's Ann. der Chem. u. Pharm., 28, 332 (1838).

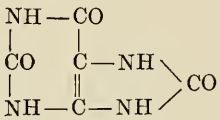
Amorphous and Crystalline Uric Acid. — Bird [1] thought that amorphous uric acid does not exist, and Simon [2] considered it rare.

Fritzsch [3] showed that if serpent's excrement be extracted with borax solution and the uric acid precipitated with HCl, according to Böttger's method [4] there is obtained a transparent crystalline hydrate of uric acid and two molecules of water, $C_5H_4N_4O_3.2H_2O$. This slowly changes to the more transparent form on standing. With pure urate solution he could not get these transparent crystals; the uric acid precipitated in a heavy flocculent amorphous form, but he believed that both forms have the same chemical composition. This amorphous variety changes to the anhydrous non-transparent crystalline modification on standing. Matignon [5] showed that this last change is accompanied by an absorption of heat, and, since Berthelot has shown that the change of a precipitate from its initial to its final state is always an exothermic change, unless there is a gain or loss in the number of molecules of water on crystallization, then Matignon's work indicates that the precipitate as first obtained is a hydrate, probably that of Fritzsch. This work should be confirmed by more careful experiments.

Attention has been called to the fact that we cannot tell whether uric acid has the lactim formula



or the lactam formula



According to Emil Fischer, both forms probably exist. The

[1] Eckstein. Bibliothek des Ausland für die organisch-chemische Ruhlung der Heilkunde, 1844, 2, 31.

[2] Simon. Beiträge zur physiologische und pathologische Chemie und Mikroscopie, 1, p. 97.

[3] Fritzsch. Ueber ein krystallisirtes Hydrat der Harnsäure. Jour. für prakt. Chem., 17, 56 (1839).

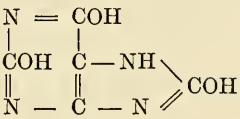
[4] Böttger. Beiträge zur Physik und Chemie, p. 6.

[5] M. Matignon. Sur l'hydrate d'acide urique. Bull. de la Soc. Chim. (3), 11, 571 (1894).

lactam formula does not explain the acid properties of uric acid; the lactim formula does. The existence of six monomethyl uric acids can be explained on the assumption that both the lactim and the lactam forms exist. Fischer thinks that the finely divided hydrate precipitated from urate by acids in cold solution, the precipitate investigated by Matignon, is a hydrate having the lactim formula, and that the anhydrous acid formed through the influence of water on standing has the lactam formula. Tunicliffe and Rosenheim [1] think that the transparent crystals obtained by Fritzsch represent an intermediate stage between the lactim and the lactam formula.

THE URATES

The lactim formula of uric acid



is the one which accounts for its acid properties. There are three hydrogen atoms which we might possibly suppose replaceable by bases. We have, however, no tribasic salts. This is not strange, for often the tribasic salts of weak acids, for example, phosphoric acid, do not form in solution. The dissociation of the third hydrogen ion is comparable with the dissociation of the water, and consequently a tribasic salt would be immediately decomposed by water. We do have, however, monobasic and dibasic urates.

The urates containing two molecules of the base were called neutral urates by Bensch,[2] and those containing one atom of the base acid urates. The latter are often called biurates. Tollens [3] proposes the more rational names mono- and di-urate for the salts containing respectively one and two atoms of the base, and for the hypothetical quadriurate supposed to contain less base than the mono-urate he proposed the name hemi-urate.

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[1] Tunicliffe and Rosenheim. Contributions to our Knowledge of Uric Acid Salts. Lancet, 1900, 1708.

[2] A. Bensch. Ueber einige Salze der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 54,.189 (1845).

[3] B. Tollens. Handbuch der Praktischen Medizin. Ebstein-Schwalbe, 3, pt. 2, 588 (1901).

The Neutral Urates. — The neutral urates of potassium and sodium were first prepared by Bensch.[1] Uric acid was warmed with an aqueous solution of the base free from carbonate or carbon dioxide, and then precipitated with alcohol or evaporated down in an atmosphere free from carbonic acid, for carbonic acid decomposes the neutral urate to acid urate. Bensch, together with Allen,[1] prepared also the neutral salts of calcium, barium, and strontium, and determined their solubilities. According to these authors, neutral potassium urate is soluble in 35 parts of boiling water and 44 parts of cold water, neutral sodium urate in 77 parts of cold water, calcium urate in 1,440 parts of hot water and 1,500 parts of cold water, barium urate in 2,700 parts of hot water and 7,900 parts of cold water, and strontium urate in 1,790 parts of hot water and 4,300 parts of cold water. These neutral salts can exist only in a solution containing some of the free base. The view expressed by Ebstein [2] in his book on gout that the uric acid circulates in the blood as neutral urate must be wrong, since there is no free caustic alkali in the blood and there is plenty of carbonic acid and carbonates which would decompose the neutral urates.

The Acid Urates. — The acid urates of potassium, sodium, ammonium, calcium, magnesium, and strontium were first prepared and their solubilities determined by Bensch. Sodium acid urate is soluble in 122 parts of hot water and 1,150 of cold water, potassium acid urate in 75 parts of hot water and 790 of cold water, ammonium acid urate in 1,600 parts of boiling water, calcium acid urate in 276 parts of boiling water and 603 parts of cold water, magnesium acid urate in 160 parts of boiling water and 3,750 parts of cold water, and strontium acid urate in 2,300 parts of boiling water and 5,300 parts of cold water. The acid urate of lithium was prepared by Schilling.[3] He found it soluble in 39 parts of boiling water and 370 parts of cold water. The acid urates of potassium and sodium can be prepared by treating the neutral urate with carbonates, carbonic acid, or acid sodium phosphate, or by dissolving uric acid in an alkaline carbonate.

[1] Bensch. Ueber einiger Salze der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 54, 189 (1845).

Allen und Bensch. Ueber die neutralen Salze der Harnsäure. Liebig's Ann. der Chem. u. Pharm., 65, 181 (1848).

[2] W. Ebstein. Die Natur und Behandlung der Gicht, 98 (1882).

[3] v. Schilling. Ueber die Verbindung der Harnsäure mit Lithion. Liebig's Ann. der Chem. u. Pharm., 122, 241 (1862).

His [1] studied the alkali urates with considerable care. He found that if sodium hydroxide be gradually added to a solution of uric acid containing some uric acid in suspension, sodium acid urate is first formed. This then dissolves on addition of more sodium hydrate, forming neutral urate. According to Pfeiffer,[2] the mono-basic urates react neutral and not acid in solution, and only in the presence of strong alkalies can they change to the soluble dibasic salt, — hence the uselessness of trying to dissolve the gouty concretions of acid sodium urate with weak alkalies.

The acid urates exist in the amorphous form and in the form of crystalline needles. If acid sodium urate is precipitated quickly from solution by any means, it comes down first in the form of little balls. These are the "Kugelurates" [3] of Mordhorst, the "Sphärolithen" [4] of Ebstein and Nicolaier. These balls soon begin to bristle with points and finally change to needle-like crystals. If the acid urate is precipitated slowly, it may come down crystalline immediately.

Baumgarten [5] showed by analysis that the amorphous and the crystalline forms of the acid urate have the same chemical composition, and that as soon as the amorphous form is washed free from impurities, further washing with pure water changes it to the crystalline form. This was later confirmed by Tunicliffe and Rosenheim.[6] Mordhorst,[3] who studied them in a rough, qualitative way only, called these amorphous balls "Kugelurates." He thought he found that water and alcohol dissolve out a little alkali from them, and without proof assumed that they had a different composition from the crystalline salt and from uric acid. He believed that their composition is variable, that the amount of base in them depended upon the concentration of the base

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[1] W. His. Physikalisch-chemische Untersuchungen über des Verhalten der Harnsäure und ihrer Salze in Lösungen. Verhandl. des 18t Kongr. für innere Medizin, Wiesbaden, 425 (1900).

[2] E. Pfeiffer. Ueber Harnsäureverbindungen beim Menschen. Berl. klin. Wochenschrift, 31, 913 (1894).

[3] Mordhorst. Zur Pathogenese der Gicht. Verhandl. des 14t Kongr. für innere Medizin, 405 (1896). Also

Die Entstehung und Auflösung der Harnsäureverbindungen ausserhalb und innerhalb des menschlichen Körpers. Zeitschr. für klin. Medizin, 32, 65 (1897).

[4] W. Ebstein und A. Nicolaier. Ueber die kunstliche Darstellung von harnsäuren Salzen in der Form von Sphärolithen. Virchow's Archiv für path. Anat., 123, 373 (1891).

[5] Baumgarten. Harnsäures Natron in durchsichtigen Kugelnerscheinend. Liebig's Ann. der Chem. u. Pharm., 117, 106 (1861).

[6] Tunicliffe and Rosenheim. Contributions to our Knowledge of Uric Acid Salts. Lancet, 1900, 1, 1708.

in the solution from which they are precipitated. Ebstein and Nicolaier [1] found that they show a black cross when examined under the polarization microscope.

These amorphous urates have a far higher solubility than the crystalline forms. Ord [2] first noticed that these solutions did not act altogether like real solutions. They resemble more in some ways a fine suspension in water. These colloidal solutions were further investigated by His,[3] who showed that the acid urate would gradually precipitate out on standing, appearing first as "Kugelurate" and later changing to the crystalline form. The lithium salt shows an especially great tendency to form supersaturated solution. His thinks that this colloidal form may play some part in the body. Roberts [4] thinks this amorphous form of acid urate may be a hydrate of sodium acid urate and calls attention to the fact that, unlike colloids, generally it dializes. His method of obtaining this form of the salt is to saturate boiling water with sodium acid urate and then cool. On cooling the excess of acid urate does not separate out, but if we add common salt to the solution, it then precipitates out as a jelly, which, on standing, slowly becomes crystalline. The precipitation of the amorphous sodium acid urate is greatly hastened by sodium salts of any acid and also by uric acid. The rapidity of precipitation seems to be directly dependent on the concentration of the urate or the uric acid.

Roberts [4] has shown that when blood serum or a solution of sodium salts of the same concentration as blood serum is charged to the extent of one part to about 5,000 to 6,000 with amorphous urate, there is danger of precipitation. Garrod has found this amount of uric acid in the blood at times. Roberts further calls attention to the fact that urate deposits in gout occur in the parts rich in sodium salts. According to him, although the blood serum and the lymph are rich in sodium salts, the precipitation of acid urate would be less likely to take place than in the synovial fluid, which is more quiet. The reason why a

[1] W. Ebstein und A. Nicolaier. Ueber die kunstliche Darstellung von harnsäuren Salzen in der Form von Sphärolithen. Virchow's Archiv für path. Anat., 123, 373 (1891).

[2] Ord. On the Influence of Colloids upon the Crystalline Form and Cohesion. London, 1879, 72.

[3] W. His. Physikalisch-chemische Untersuchungen über das Verhalten der Harnsäure und ihre Salze in Lösungen. Verhandl. des 18t Kongr. für innere Medizin, 425 (1900).

[4] Sir W. Roberts. Croonian Lectures. Chemistry and Therapeutics of Uric Acid, Gravel, and Gout. Lancet, 1892.

Blood serum[1]	0.70%
Lymph	0.70%
Synovia	0.80%
Cartilage	0.90%
Fibrous tissue	0.70%
Blood corpuscles	0.20%
Brain	0.20%
Muscle	0.08%
Spleen	0.04%
Liver	0.02%

deposit occurs in one joint and not in another is ascribed by him to the variations in the composition of the synovial fluid of different joints. Frenihs[2] finds that the joints of resting animals contain more synovial fluid than those of working animals, and that it is rich in mineral salts, especially sodium salts. This, he thinks, might have some connection with the fact that gouty people are often inactive. Dastre and Loye[3] have shown that the concentration of the blood in NaCl does not vary much. In case of a temporary decrease in the amount of NaCl in the food, this salt is extracted from the tissues to make up the deficit. In case the salt in the food is especially high, it is temporarily stored up in the synovia until it can be excreted by the kidneys. In case of gout, then, it might be well to keep the common salt in the food from running too high, according to Roberts, who says that mineral waters high in sodium salts often provoke an attack of gout almost immediately after the patient begins to take them.

Ebstein[4] states in his book on gout that neutral sodium urate circulates in the blood, and that this under the influence of acid crystallizes out as the monosodium urate and gives the gouty concretion. This cannot be true, for Pfeiffer[5] has shown that monosodium urate can form only in an alkaline solution and that the rate of formation of the acid sodium urate depends on the richness of the solution in alkaline salts. Another condition necessary for the formation of acid sodium urate is the presence of carbon dioxide and carbonates. If the acid salt is precipitated quickly in large amounts, the "Kugelurate." is thrown down first and slowly changes to the crystalline needle form. If the precipitation is slow, the needles are formed directly. The formation of this salt in an acid solution, as well as its further existence in such a solution, is impossible. Acids change it immediately to its components, free uric acid and the base. This salt cannot, therefore, come down from acid urine.

[1] Munk and Rosenstein. Maly's Jahresbericht, Vol. XX, p. 40.

[2] Frenihs. Wagner's Handwörterbuch d. Physiol., Vol. III, pt. 1, p. 463.

[3] Dastre et Loye. Lavage du Sang. Archives de Physiologie, 1888, p. 93.

[4] W. Ebstein. Die Natur und Behandlung der Gicht, 1882.

[5] E. Pfeiffer. Ueber Harnsäureverbindungen beim Menschen. Berl. klin. Wochenschrift, 31, 913 (1894).

Roberts [1] found sodium acid urate soluble in about 1,000 parts of water, but in 10,000 parts of blood serum. He found that if the salts are dialized out, the serum then dissolves the urate as readily as pure water. In an aqueous solution of the blood-salts having the same concentration as the blood itself, the acid urate has the same solubility as in the blood. Sodium chloride and sodium carbonate are the chief salts of the blood, and Roberts found that an aqueous solution of these of the same strength as found in the blood dissolves just as much uric acid as the blood serum. He showed further that all sodium salts, even the alkaline phosphate and carbonate and the salicylate, decrease the solubility of the acid urate enormously. The power of the different salts in equi-molecular solution in this respect is about the same. Potassium salts have no effect on the solubility of the acid urate of sodium. Magnesium, calcium, and ammonium salts decrease the solubility of the urate. Experiments with the carbonate of potassium and lithium showed that these and also piperazin do not make sodium acid urate any more soluble in blood serum.

A priori we should expect that the solubility of sodium acid urate in salt solutions would be just as Roberts showed. His [2] has explained the facts from the laws of electrolytic dissociation. In the same manner that acids, by increasing the concentration of the hydrogen ions in a solution, decrease the dissociation and therefore the solubility of uric acid, so sodium salts, by increasing the concentration of the sodium ions, decrease the dissociation and therefore the solubility of the sodium acid urate.

Sodium acid urate in solution is partly dissociated into the positive sodium ion and the negative uric acid ion $C_5N_3H_3O_3$, and the relation between them and the undissociated portion of the urate is determined by the equation $\frac{P \times N}{U} = K$ where P stands for the concentration of the positive ion Na, N for the concentration of the negative uric acid ion $C_5N_3H_3O_3$, and U for the concentration of the undissociated portion of the urate. In a saturated solution U is a constant, and the equation becomes $P \times N = KU$, where KU is a constant. If we add a sodium salt,

[1] W. Roberts. On the History of the Uric Acid in the Urine. Medico-Chirurgical Transactions, 73, 245 (1890).

[2] W. His. Physikalisch-chemische Untersuchungen über das Verhalten der Harnsäure und ihrer Salze in Lösungen. Verhandl. des 18t Kongr. für innere Medizin, Wiesbaden, 425 (1900).

for example, NaCl or Na_2CO_3, the increase in the concentration of the sodium ion P will cause a decrease in N, the concentrations of the negative uric acid ion, in order that the product $P \times N$ remain constant. In other words, if a sodium salt be added to a saturated solution of sodium acid urate, we should expect, theoretically, a decrease in the concentration of the dissociated urate, and, since in a saturated solution at any given temperature the concentration of the undissociated portion of the uric acid is a constant, a decrease in the concentration of the undissociated urate means a decrease in the solubility of the salt itself. As we have seen, Roberts showed that sodium salts do decrease enormously the solubility of sodium acid urate. A solution of common salt of so low a concentration as 0.7 per cent decreases the solubility of sodium acid urate to about one tenth its value in pure water. Since all sodium salts have this action it is useless to attempt to dissolve gouty concretions by administration of bicarbonate of soda. In this connection it might also be mentioned that Jones found by experiment that ammonium salts in the same way lessen the solubility of ammonium urate and precipitate it from solution.[1]

Vicario [2] has studied the solubility of a number of the more soluble salts of uric acid, and gives the following results:

100 cc. of water dissolves	Grams of Salt at 18°	at 37°
Acid sodium urate	0.088	0.172
Neutral sodium urate	1.695	2.806
Acid potassium urate	0.150	0.290
Neutral potassium urate	2.320	2.553
Acid lithium urate	0.258	0.276
Neutral lithium urate	1.505	2.055
Acid calcium urate	0.175	0.205
Neutral calcium urate	0.070	0.065
Propylamin urate	0.285	0.426
Ethylendiamin urate	0.520	0.705
Urotropin urate	0.633	2.200
Piperazin urate	2.223	2.270
Lysidin urate	4.195	5.663
Dimethylpiperazin urate	5.370	6.086

Since the solubility of sodium acid urate is only one part in about 1,000, the salts of potassium, lithium, piperazin, etc., have

[1] H. B. Jones. On the State in which Uric Acid Exists in the Urine. Lancet, 1843, 366.

[2] A. Vicario. De la valeur comparée des principaux dissolvants de l'acide urique. Journ. Pharm. Chim., 6, 15, 265 (1902).

been administered in the hope of making gouty concretions more soluble. The uselessness of this plan can be seen from the following considerations: A saturated solution of sodium acid urate to which has been added a lithium salt, for example LiCl, contains the positive ions Na and Li, and the negative ions Cl and $C_5H_3N_3O_3$ with also a very little of the undissociated salts. The solubility constant K for the sodium acid urate is the same in this case as when there is nothing but sodium acid urate present, and in a saturated solution we have $P \times N = KU$ (a constant). N, that is, the concentration of the dissociated uric acid, and that means practically the solubility of the uric acid, since in such a dilute solution of urates the dissociation is practically complete, cannot increase, for immediately P would have to decrease and sodium acid urate would crystallize out. In other words, the presence of the lithium does not enable more uric acid to remain in solution. This again agrees with the experimental evidence of Roberts that potassium and lithium salts do not increase the solubility of the sodium acid urate. In other words, the solubility of the urates is determined by the solubility of the least soluble urate present. From this we should expect that salts of calcium, magnesium, and barium, whose urates are less soluble than that of sodium, would decrease the solubility of monosodium urate, and again Roberts showed that this is the case. It has, in fact, been shown that even very large doses of potassium and lithium salts do not increase the excretion of uric acid in gout. Piperazin, which forms a salt with uric acid soluble in 50 parts of pure water,[1] does not dissolve uric acid in the urine.[2] The same is true of lysidin, which forms a salt soluble in 6 parts of pure water.

Carbonic acid causes uric acid to precipitate from a solution of monosodium urate. In a solution of sodium acid urate to which carbon dioxide has been added, we have among other things some negative uric acid ions from the dissociated urate, and some hydrogen ions from the carbonic acid. Carbon dioxide in solution forms carbonic acid, H_2CO_3, and this dissociates in part to

[1] Biesenthal und Schmidt. Piperazin bei Gicht- und Steinleiden. Berl. klin. Wochenschrift, 28, 1214 (1891).

[2] Mendelsohn. Ueber Harnsäurelösung insbesonderer durch Piperazin. Berl. klin Wochenschrift, 29, 884 (1892).

M. Mendelsohn. Die Verschiedenheit des Problems der Harnsäureauflösung bei gichtischen Ablagerungen und bei Konkretionem in den Harnwegen. Deutsche Med. Wochenschrift, 21, 283 (1895).

the positive H ion and the negative CO_3 ion. When the concentration of the hydrogen ions is great enough to give with the negative uric acid ions a product which reaches the value KU in the equation $P \times N = KU$, uric acid begins to precipitate out. The precipitation of monosodium urate from a solution of the neutral urate can be explained in a somewhat similar way.

The Quadriurate. — The question of the existence of a third kind of urate, the so-called quadriurate or hemiurate, containing half as much of the base as the acid urate, that is, one atom of the base to two molecules of uric acid, is somewhat connected with the question of the composition of the amorphous urate deposit in urine. It was the study of this amorphous deposit which first led to the belief that a third kind of urate exists.

Berzelius,[1] the first who mentions the subject, thought that the uric acid in the urine existed in the free condition. He noticed the formation of uric acid crystals on treatment of the sediment with water. Lehmann[2] later identified these crystals as free uric acid.

Proust,[1] one of the first writers on the subject, at first thought the deposit a real acid, which he called "acide rosacique." Later, he believed that it was uric acid contaminated with coloring matter. Prout[3] believed it to be ammonium urate, and said that uric acid is dissolved in urine as ammonium urate. Donné agreed with Prout. Quevenne[4] believed it to be either a hydrate of uric acid or a compound of uric acid with coloring matter and contaminated with a little ammonia. Wetzlar[5] and Schultens,[6] without any proof, believed it was sodium urate. Duvernoy[7] said it was not ammonium urate, but uric acid contaminated with coloring matter. He ascribed to the coloring matter the property of holding uric acid in solution, and thought the precipitation was due to a change in the composition of the coloring matter. But Prout, in his book just mentioned, shows that the colorless serpent excrement is as soluble as the urine deposit, so that Duver-

[1] Berzelius. Lehrbuch der Chemie.

[2] Lehmann. Lehrbuch des physiologische Chem., Vol. II, p. 355.

[3] Prout. On the Nature and Treatment of Stomach and Renal Diseases. London, 1843, p. 188.

[4] L'Heritier. Chimie pathologique, 1842.

[5] Wetzlar. Beiträge zur Kenntniss des menschlichen Harn und der Entstehung der Harnsteine.

[6] Schultens. Neues Journal der Chemie, Vol. III, p. 347.

[7] Duvernoy. Chemische-medicinische Untersuchungen über den menschlichen Urin, 1835, p. 20.

noy's view must be wrong. Willis [1] said that the solubility of uric acid in urine is due to the formation of a soluble hydrate, but Fritzsch has shown that on adding acid to a urate it is the hydrate of uric acid which first precipitates, so that the hydrate is insoluble. Becquerel [2] agreed with Quevenne, and thought that the deposit is uric acid with impurities of coloring matter and perhaps a little ammonium salt.

Scherer [3] said that the uric acid is in the urine as sodium urate, and that the deposit is uric acid set free by lactic acid. Lipowitz [3] agreed with Scherer. Liebig and Heintz [4] showed that the urine does not normally contain any lactic acid, so that both Scherer and Lipowitz are wrong.

Heintz [5] showed the presence of potassium, sodium, ammonium, and often calcium and magnesium, in the red amorphous urine deposit. He noticed that there is considerably more uric acid in the deposit than can be accounted for by assuming that it is all united with the bases in the form of acid urate, and succeeded in obtaining a body or mixture of bodies which corresponded somewhat with a quadriurate formula, that is, contained half as much base as the acid urate.

Von Scherer [6] said that in the amorphous urine sediment there is no crystalline uric acid, but there is sodium, and also more uric acid than can be accounted for by assuming that it is all combined as acid urate. He did get sediments in which the excess of uric acid over that necessary to form urate was somewhere near half the total uric acid. But he called attention to the fact that amorphous urine sediment and the sediment obtained by mixing acid urate and neutral phosphate of soda always contains some sodium phosphate, no matter how much we may attempt to purify. He says that the amount of sodium in the deposit depends on the amount of acid sodium phosphate in the urine, and thinks that the sediment is a mixture of uric acid and acid sodium urate. His artificial deposit is obtained by adding uric

[1] Willis. Krankheiten des Harnsystems, 1841, p. 20.

[2] Becquerel. Semiotiques des urines, 1841, p. 45.

[3] Lipowitz. Simon's Beiträge zur physiologische und pathologische Chemie und Mikroskopie, 1, 97.

[4] Liebig und Heintz. Ueber eine neue Säure im menschlichen Harn. Poggendorf's Annal., 62, 602 (1844).

[5] W. Heintz. Ueber die Harnsäuren Sedimente. Müller's Arch. für Anat. Physiol. und Wissenschaftl. Medizin, 1845, 30.

Ueber die harnsäuren Sedimente. Liebig's Ann. der Chem. u. Pharm., 45, 55 (1845).

[6] Von Scherer. Jahresbericht über die Fortschritte in der Biologie, 1845, 156.

acid to a warm solution of disodium phosphate which has been made nearly neutral with phosphoric acid and then cooling. This is the method used by later experimenters to obtain artificial urine sediment. It gives a precipitate which resembles the urinary deposit very much.

Jones was the next to study the urinary sediment. At first [1] he believed it to be ammonium urate. Later [2] he took another view. He worked mostly with sediment prepared artificially from disodium urate and uric acid. He noticed that no uric acid crystals can in most cases be found in the amorphous sediment, that there is considerably more uric acid in the sediment than can be accounted for by assuming that it is all combined as biurate, and that on treating the sediment with distilled water after washing out impurities, some uric acid crystals are formed.

From the amount of sodium and the total amount of uric acid found by Scherer in his analyses, Jones calculated the ratio between the amount of uric acid in each case needed by the sodium to form acid urate and the excess of uric acid in the sediment, and found this to be in four cases, respectively, 1:2.04, 1:0.17, 1:0.42, and 1:2.08. This gives an average of 1:1.18. Jones himself prepared a few sediments and found this ratio in three cases to be: 1:1.72, 1:0.46, and 1:1.04. These ratios give an average of 1:1.07. He assumed that the averages of these two sets of results were near enough to each other and near enough to the ratio of 1:1 to be called 1:1. Many of his sediments gave discordant results. In some cases the sediment seemed to be practically all uric acid; in other cases it nearly all dissolved and only contained enough uric acid to combine with the sodium as acid urate. Such cases, however, he rejected as faulty in his calculations. From all these facts he assumed that there is sometimes in urinary sediment a body whose formula may be written $NaC_5H_3N_4O_3 + C_5H_4N_4O_3$. This, he said, is an unstable body, easily decomposed by water into uric acid and sodium acid urate.

Jones had no right to assume that there is a chemical compound that contains half as much sodium as the monosodium urate. In the first place, on account of the fact that under the micro-

[1] H. B. Jones. On the State in which the Uric Acid Exists in the Urine. Medico-Chirurgical Transactions, 1844, 102.

[2] *Ibid.* On the Composition of the Amorphous Deposit of Urates in Healthy Urine. Journ. of the Chem. Soc., London, 1862, 201.

scope he could not see any crystals of uric acid, he said that there is no free uric acid in the sediment. But Fritzsch,[1] Matignon,[2] and His [3] have shown that uric acid can exist in the amorphous form, a form in which condition, of course, Jones could not recognize it under the microscope. These same authors have likewise shown that the amorphous uric acid becomes crystalline on standing in water, just what happened in the work of Scherer and Jones. Jones thought, however, that this formation of crystals was due to the appearance of uric acid set free from the quadriurate. In the next place, the ratios between the uric acid necessary to combine with the sodium in the sediment and the excess are so discordant that an average means absolutely nothing. Besides, their method of determining uric acid by precipitation with HCl has been shown to be very much in error. Again, their ratio in any case was not 1:1.0 or anywhere near it. Further, Scherer showed that the sediment always contains sodium phosphate, and finally, Jones threw out, without any right to do so, those of his experiments in which the ratio between the combined and the free uric acid did not agree well with his theory.

Roberts,[4] in 1890, made a study of the natural and artificial urinary sediments, and later elaborated the results of the work in his Croonian [5] lectures. He agreed with Jones that salts of uric acid containing half as much of the base as the biurate and easily decomposed by water exist. He went further and stated that the quadriurate of sodium is the form in which the uric acid exists in the urine and in the blood.

Roberts reviewed the work of Jones without, however, the proper criticism, and then by a few experiments showed that the excrement of birds and reptiles was similar to the amorphous sediment of human urine. This sediment, on treatment with a large quantity of water, gives uric acid crystals and also sodium biurate. The sodium biurate goes into solution. He found the sediment so impure, however, that the quantitative

[1] Fritzsch. Verbindung von Harnsäure mit Schwefelsäure. Liebig's Ann. der Chem. u. Pharm., 28, 332 (1838).

[2] M. Matignon. Sur l'hydrate d'acide urique. Bull. de la Soc. Chim. (3), 11, 571 (1894).

[3] W. His. Physikalisch-chemische Untersuchungen über das Verhalten der Harnsäure und ihrer Salze in Lösungen. Verhandl. des 18t Kongr. für innere Medizin, 425 (1900).

[4] W. Roberts. On the History of the Uric Acid in the Urine. Medico-Chirurgical Transactions, Vol. LXXIII, 245 (1890).

[5] *Ibid.* Chemistry and Therapeutics of Uric Acid Gravel and Gout. (Croonian Lectures.) Lancet, 1892.

relations between the sodium and the uric acid were never such that he could assume that the quadriurate was certainly present. He, therefore, prepared artificial sediment by treating a solution of uric acid in sodium hydroxide with acetic acid. By this method he obtained a granular precipitate which looked somewhat similar to ordinary amorphous urinary sediment, but which was colorless. He washed it a little with alcohol, and then treated it with a large quantity of distilled water. After a while, the water extracted from the sediment sodium acid urate and left behind crystalline uric acid. The amount of crystalline uric acid and also the amount of uric acid which went into solution was determined by precipitation with acid, and the ratio of the former to the latter was found in two cases to be as 1:1.27 and 1:1.12, respectively. He then made a number of analyses of artificial sediments obtained by this and other methods and found that the amount of acid and alkali in the solution has to be very carefully adjusted in order to get a sediment the composition of which corresponds to a quadriurate formula. If the solution were too strongly acid, he obtained a sediment which contained too much uric acid. If the solution were too strongly alkaline, the sediment contained too little uric acid.

By carefully selecting pieces of bird's urine he succeeded in getting a couple of samples in which the ratio of the combined uric acid and the free was within a few per cent of 1:1. With serpent's urine he could not find any such ratio.

E. Pfeiffer[1] showed that the sediment obtained by Roberts' method always contains phosphate of sodium even after repeated washing and even after the final alcoholic or aqueous washing appears to be free from phosphate. He showed that if an artificial precipitate is obtained by Roberts' method, — precipitation from sodium phosphate solution, — it contains sodium, phosphoric acid, and uric acid, and according to the reaction of the solution there is obtained a sediment rich in sodium and phosphate acid and poor in uric acid, or the reverse, or a sediment containing sodium and uric acid in any of the intermediate ratios. When a precipitate is obtained which contains sodium and uric acid in the proportion to form a quadriurate, it is due to accident or to careful adjustment of the conditions. He calls attention to the

[1] E. Pfeiffer. Ueber Harnsäureverbindungen beim Menschen. Berl. klin. Wochenschrift, 31, 913 (1894).

fact that neither Jones nor Roberts found any quadriurate in natural urinary sediment.

Warnecke[1] has recently reaffirmed what has been known for thirty years, that Heinze's method for the determination of uric acid, the method used by Jones and also by Roberts, is very far from accurate.

Again, in treating the sediment with water to decompose the quadriurate and dissolve out the acid urate, nearly six per cent of the free uric acid is dissolved. Roberts corrects for this, but does not take it into account when he determines the combined uric acid in the solution.

Besides this large error, there is another due to the fact that in his determination of uric acid, Roberts dried it at a temperature of 37°. Tunicliffe and Rosenheim[2] have shown that a large amount of water is still retained by the acid after heating at this temperature. These authors confirm the view of Pfeiffer[3] that in the artificial sediment the ratio between the free and the combined uric acid is very variable. They say that the sediment is a mixture of sodium acid urate, uric acid, and water. A mixture of amorphous uric acid with amorphous acid urate was shown by them to act like the so-called quadriurate sediment. The urate went into solution and the uric acid became crystalline.

There seems no question, then, that the so-called quadriurates are mixtures of acid urate with varying amounts of uric acid. On treatment with large quantities of water, the acid urate goes into solution and the amorphous uric acid becomes crystalline. This is what happens when either of these bodies alone is treated with water, or when a mixture of the two is so treated.

His[4] has explained the precipitation of the mixture of uric acid and acid urate. On addition of carbonic acid to a solution of urate, as we have seen, the acid urate first precipitates, on account of the solution becoming saturated with it. On further addition of carbonic acid, when the product of the negative uric acid ions and the hydrogen ions from the carbonic acid reaches

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[1] Warnecke. Dissertation, Göttingen, 1898.

[2] Tunicliffe and Rosenheim. Contributions to our Knowledge of Uric Acid Salts. Lancet (1900), 1, 1708.

[3] E. Pfeiffer. Ueber Harnsäureverbindungen beim Menschen. Berl. klin. Wochenschrift, 31, 913 (1894).

[4] W. His. Physikalisch-chemische Untersuchungen über das Verhalten der Harnsäure und ihrer Salze in Lösungen. Verhandl. des 18t Kongr. für innere Medizin, Wiesbaden, 1900, 425.

the value of the solubility constant for uric acid, then free uric acid precipitates.

Compounds of Uric Acid with Urea and Kreatin. — Rüdel[1] states that the presence of urea increases the solubility of uric acid in water or in urine, and that the uric acid from this compound, unlike the uric acid in urates, is not easily precipitated with acids. His experiments seem to show this. He prepared a body which on analysis gave results that approximated the formula $C_5H_4N_4O_3 + CO(NH_2)_2 + H_2O$, a compound of one molecule of uric acid, one molecule of urea and one molecule of water of crystallization. In the same article he reached the conclusion that uric acid is more soluble in dilute HCl than in water. The latter conclusion has been shown theoretically not probable, and, in fact, certainly experimentally wrong, by His.[2] Neither His[2] nor Klemperer[3] could confirm the existence of a compound of uric acid and urea, and His[2] found that urea does not increase the solubility of uric acid in water. From the work of Rüdel it has been assumed by many physicians that urea increases the solubility of uric acid in blood likewise, and a large meat diet has therefore been recommended by these men in gout. It has even been suggested to give 10 to 15 grams of pure urea. The work of His[2] and Klemperer[3] has shown that there is no basis for this. Klemperer found that kreatin forms a compound with uric acid, but His[4] has shown that this is merely an ordinary salt decomposed by acids like the salt of piperazin and uric acid.

Compounds of Uric Acid with Nucleic and Thymic Acids and Formaldehyde. — Kossel[5] showed that nucleic acid combines with the purin bases and forms a soluble body from which ammoniacal silver nitrate solution does not precipitate the base. Kossel and Neumann[6] showed that thymic acid acts in the same

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[1] Rüdel. Zur Kenntniss der Lösungsbedingungen der Harnsäure in Harn. Arch. für exp. Path. u. Pharm., 30, 469 (1892).

[2] W. His. Physikalisch-chemische Untersuchungen über das Verhalten der Harnsäure und ihrer Salze in Lösungen. Verhandl. des 18t Kongr. für innere Medizin, Wiesbaden, 1900, 425.

[3] Klemperer. Harnsäure Kreatinin eine wasserlöslich Harnsäureverbindungen. Fortschritte Mediz., 19, 328.

[4] W. His. Die Harnsäureablagerungen des Körpers und die Mittel zu ihrer Lösung. Therapie der Gegenwart, Neue Folge, 3, 434 (1901).

[5] Kossel. Du Bois Reymond's Archiv für Physiologie, 1893. Remark.

[6] A. Kossel und A. Neumann. Ueber Nucleinsäure und Thyminsäure. Zeitschr. für physiol. Chem., 22, 81 (1896).

way. This led Goto[1] to study the action of nucleic and thymic acids on uric acid. If we add the sodium salt of thymic acid to a solution of uric acid in sodium hydroxide, and then acidify the solution with HCl, a large amount of uric acid stays in solution even on standing a couple of days. From a similar solution containing no thymic acid, the HCl precipitates all but a small fraction of the uric acid. We know that carbon dioxide precipitates sodium acid urate from a solution of uric acid in sodium hydrate. But if we add some of the sodium salt of thymic acid to a solution of neutral sodium urate and then attempt to precipitate sodium acid urate with carbon dioxide we find that an exceedingly large amount of sodium acid urate stays in solution. In other words, we find that nucleic acid and thymic acid increase the solubility of sodium acid urate in water, and that acids do not precipitate the uric acid from the solutions. In a remark after the paper of His,[2] Minkowski stated that he had prepared independently a soluble compound of nucleic acid and uric acid and suggested that this may be the combination in which uric acid circulates in the blood. He stated that he might publish the details of his work later, but I cannot find that he has done so.

Goto did but a few experiments and the differences in solubility in the presence and in the absence of thymic and nucleic acids were not very large. Further, in some of the experiments, uric acid seemed to precipitate gradually on standing even in the presence of the nucleic and thymic acids.

His [3] has prepared a similar soluble compound of formaldehyde and uric acid from which the uric acid is not precipitated by acids, and he believes that there may well be a large number of bodies which combine similarly with uric acid, among which we may find a body which will be of therapeutic value in dissolving uric acid. Urotropin which decomposes in the body and gives

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[1] Kossel und Goto. Sitzungberichte der Gesellschaft zur Beförderung der Naturwissenschaften. Marbung, 1900. Also

M. Goto. Ueber die Lösung der Harnsäure durch Nucleinsäure und Thyminsäure. Zeitschr. für physiol. Chem., 30, 473 (1900).

[2] W. His. Physikalisch-chemische Untersuchungen über das Verhalten der Harnsäure und ihrer Salze in Lösungen. Verhandl. des 18t Kongr. für innere Medizin, Wiesbaden, 1900, 425.

[3] *Ibid.* Die Harnsäureablagerungen des Körpers und die Mittel zu ihrer Lösung. Therapie der Gegenwart, Neue Folge, 3, 434 (1901).

formaldehyde which combines with uric acid was introduced as a therapeutic agent by Nicolaier.[1]

Uric Acid in the Urine

The behavior of the uric acid in the urine has not previously been fully explained. The laws of physical chemistry, however, give us a full explanation of the precipitation of uric acid when urine cools, and the effect of drugs on the solubility of uric acid in the urine. The earliest explanation was that the precipitation of uric acid on cooling is due simply to a decrease in solubility. Robin and Verdeil [2] state that uric acid is soluble in 2,000 parts of urine. When there is more uric acid present it crystallizes out. Prout [3] and Bartels,[4] however, knew that a precipitation of uric acid in the urine did not mean an increased excretion.

The most widely spread view is that the uric acid in the urine exists as sodium acid urate. On account of the fact that mineral acids do not promptly precipitate all the uric acid from solution in urine, Camerer [5] thought that a part of the uric acid must be combined with some other organic compounds, giving a body which is not decomposed by acids.

Rüdel [6] states that he prepared two compounds of urea and uric acid which were easily soluble, and that he found that large amounts of urea increase the solubility of uric acid in urine.

His [7] repeated the experiments of Rüdel, but was not able to prepare a compound of urea and uric acid. He showed that the slow precipitation of the uric acid from urine by acids is due to the fact that when the uric acid is set free from the urate by acid, a supersaturated solution of acid is formed which changes only slowly to a real solution and gives a precipitation of practically the whole of the uric acid. The supersaturation of a solu-

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[1] A. Nicolaier. Ueber die therapeutische Verwendung des Urotropin (Hexamethylentetramin). Deutsche Med. Wochenschrift, 21, 541 (1895).

[2] C. Robin et F. Verdeil. Traité de chimie anatomique et physique. Vol. II, 399, 1853, Paris.

[3] Prout. On the Nature and Treatment of Stomach and Renal Diseases. London, 1848.

[4] Bartels. Untersuchungen über die Ursachen einer gesteigerten Harnsäure-Ausscheidung in Krankheiten. Deutsche Arch. für klin. Med., 1, 13 (1865).

[5] W. Camerer. Zur Lehre von der Harnsäure und Gicht. Deutsche Med. Wochenschrift, 17, 356 (1891).

[6] G. Rüdel. Zur Kenntniss der Lösungsbedingungen der Harnsäure im Harn. Arch. für exp. Path. u. Pharm., 30, 469 (1892).

[7] W. His. Die Harnsäureablagerungen des Körpers und die Mittel zu ihrer Lösung. Therapie des Gegenwart, Neue Folge, 3, 434 (1901).

tion with any substance does not continue when some of the solid substance is present, the rapidity of precipitation being dependent on the intimacy of mixture of the solution and solid and on the extent of surface offered by the solid to the liquid. In Heinze's method of determining uric acid in urine, by precipitation with hydrochloric acid, large crystals of uric acid are formed which fall to the bottom or stick to the sides of the beaker in which the determination is made. Hence sometimes complete precipitation does not occur for weeks. His succeeded in precipitating all the uric acid from urine to which hydrochloric acid was added by adding a very little and practically negligible amount of finely divided uric acid and rotating the solution for a day or so. The determination of the uric acid in this way gave results which agreed closely with the results obtained by the Salkowski method. This shows that the uric acid in the urine is all combined as an ordinary salt and not organically combined, and that conclusions arrived at by physico-chemical methods in pure urate solutions can be applied to the urine.

The theories of Roberts, Jones, and others concerning the behavior of the quadriurates in the urine are of no value, since the quadriurates have been shown not to exist. This subject has already been discussed at length.

When urine stands, there may occur a precipitation of crystalline uric acid which does not redissolve on warming, or a precipitate of amorphous sodium or ammonium urate which redissolves on warming. The latter gradually changes to crystalline uric acid on standing. A small amount of magnesium urate has been found in the sediment by Salkowski,[1] and a small amount of calcium urate by Délépine.[2] The old view expressed by Scheube,[3] that the precipitation of uric acid is due to high acidity and high concentration of uric acid was the prevailing view of a generation ago.

This precipitation is partly due to the fact that the urates are more soluble at the body temperature than at the room temperature, but in greater part to chemical reaction.

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[1] E. Salkowski. Ueber die Bildung von flüchtigen Fettsäuren bei der ammoniakalischen Harngährung. Zeitschr. für physiol. Chem., 13, 272 (1889).

[2] S. Délépine. Ueber Calciumurate. Maly's Jahresb. über die Fortschritte der Thierchemie, 18, 113 (1888).

[3] B. Scheube. Die Harnsäureausscheidung und Sedimentbildung bei croupöser Pneumonie. Arch. der Heilkunde, 17, 185 (1875).

Camerer [1] showed that if we mix a saturated solution of acid sodium urate with a solution of acid sodium phosphate at 37°, a mixture which reacts acid to litmus paper, and allow it to cool, the solution becomes alkaline, and crystals of uric acid appear. The following reaction takes place:

$NaC_5H_3N_4O_3$	+	NaH_2PO_4	=	$C_5H_4N_4O_3$	+	Na_2HPO_4
sodium acid urate	+	sodium acid phosphate	=	uric acid	+	alkaline sodium phosphate

Voit and Hofmann [2] have shown that when urine cools and uric acid precipitates, the acidity of the urine decreases. They showed that if equivalent amounts of sodium acid urate and sodium acid phosphate be mixed, the acid mixture becomes alkaline, and uric acid precipitates. On this account, and on account of the fact that urine always contains acid sodium phosphate, Camerer and Voit and Hofmann assumed that the same reaction takes place in urine that takes place in the artificial solution.

The view of Voit and Hofmann that the uric acid becomes less acid on cooling cannot be accepted, for until very recently the acidity of urine had not been determined with any approach to accuracy. The titration and precipitation methods of Maly,[3] Freund,[4] Freund and Töpfer,[5] Lieblein,[6] Oliviero,[7] Berlioz, Lepinos, and Michel,[8] de Jager,[9] Naegeli,[10] Arnstein,[11] and others gave results which have no relation to the true acidity, which is the concentration of the hydrogen ions. The acidity of the urine is probably

[1] W. Camerer. Zur Lehre von der Harnsäure und Gicht. Deutsche Med. Wochenschrift, 17, 356 (1891).

[2] Voit und Hofmann. Ueber das Zustandkommen der Harnsäuresedimente. Sitzungsber. d. Kngl. bayerische Akad. de Wissenschaft, 1, 279 (1867).

[3] R. Maly. Eine Methode zur alkalimetrische Bestimmung der Phosphorsäure und der alkalischen Phosphate. Zeitschr. für analytische Chem., 15, 417 (1876).

[4] E. Freund. Ueber eine Methode zur Bestimmung von einsachsäuren Phosphate neben zweisach-säuren Phosphate im Harne. Centralbl. für die Med. Wissenschaften, 30, 689 (1892).

[5] E. Freund und G. Töpfer. Ueber die Bestimmung der Alkalinität und Acidität des Urins. Zeitschr. für physiol. Chem., 19, 84 (1894).

[6] Lieblein. Ueber die Bestimmung der Acidität des Harns. Zeitschr. für physiol. Chem., 20, 52 (1895).

[7] Oliviero. Rep. de Pharmac. (1897) 7 (Naegeli).

[8] Berlioz, Lepinos, and Michel. Chem. Ztg. Repertor, 1897 (Naegeli).

[9] L. de Jager. Ueber die Reaktion des Harnes. Zeitschr. für physiol. Chem., 24, 303 (1898).

[10] O. Naegeli. Zur Aciditätsbestimmung des Urins. Zeitschr. für physiol. Chem., 30 313 (1900).

[11] R. Arnstein. Ueber die Aciditätsbestimmung im Harn. Zeitschr. für physiol. Chem., 34, 1 (1901).

due in great part to NaH_2PO_4. This is a very weak acid. It dissociates primarily into the positive ion Na and the negative ion H_2PO_4. The negative ion H_2PO_4 dissociates partly into the negative ion HPO_4 and the positive ion H. It is to the hydrogen ions from this source that the acidity of the urine is probably due in large part. The dissociation of H_2PO_4 into H and HPO_4 is only very slight, not at all comparable even to the dissociation of hippuric or benzoic acids, for Donath [1] has shown that either of these acids can change Na_2HPO_4 completely to NaH_2PO_4.

If we attempt to determine the acidity of urine by titration, and add a little sodium hydrate, the hydroxyl ions from the sodium hydrate immediately combine with the hydrogen ions from the acid phosphate or other acid [2] to form undissociated water, for the small size of K in the equation $\frac{C_H \times C_{OH}}{C_{HOH}} = K = .64 \times 10^{-14}$ makes it impossible for more than an insignificant quantity of hydrogen ions and hydroxyl ions to exist together in solution. But as soon as these hydrogen ions begin to disappear more are set free from the ion H_2PO_4 in order that the equilibrium expressed by the equation $\frac{C_H \times C_{HPO_4}}{C_{H_2PO_4}} = K$, where C_H, C_{HPO_4}, and $C_{H_2PO_4}$ are the concentrations of hydrogen, HPO_4 and H_2PO_4 ions, respectively, may be maintained. This dissociation of H_2PO_4 continues as the titration proceeds until all the H_2PO_4 has broken up into HPO_4 and H. Titration of a urine with sodium hydroxide therefore determines the concentration of the hydrogen ions, that is, the acidity, plus the concentration of the H_2PO_4 plus the concentration of the other acid bodies. This same objection applies to all titration and precipitation methods. Bugarsky and Liebermann [3] first applied a principle found in Nernst's textbook on physical chemistry to the analysis of physiological fluids. This method was modified by Rhorer [4] and

[1] Donath. Sitzungsber. d. Wiener Akad., 1874.

[2] In the following discussion concerning the acidity of the urine, H_2PO_4 is used for brevity to represent the acids of the urine other than uric acid. It is probably the principal acid present.

[3] L. Bugarsky und L. Liebermann. Ueber das Bindungsvermögen eiweissartiger Körper für das Salzsäure Natrium. Pflüger's Archiv, 72, 51 (1898).

[4] L. Rohrer. Die Bestimmung der Harnacidität auf elektrometrischem Wege. Pflüger's Archiv, 86, 586 (1901).

by Höber [1] and applied to urine and blood analysis. The principle of the method, in brief, depends upon the fact that if we have an acid solution, of urine, for example, in contact with a solution of dilute hydrochloric acid, there will be a difference of potential between the urine and the acid. The difference in potential depends upon the ratio $C_a : C_b$, where C_a is the concentration of the hydrogen ions in the hydrochloric acid, and C_b the concentration of the hydrogen ions in the urine. We can measure the difference in potential, determine C_a and from these calculate C_b. How little reliance can be placed on conclusions concerning the acidity of the urine determined by titration methods may be seen from the fact that while the titration methods give urine an average acidity of about $\frac{N}{30}$, the electrochemical methods give the concentration of hydrogen ions an average of about 30×10^{-7} (Rohrer [2]) and 15×10^{-7} (Höber and Jankowsky [3]). This would indicate that the titration methods give a result from 10,000 to 20,000 times too high.

Zerner [4] found that uric acid is precipitated by monosodium phosphate only when there is no neutral phosphate in excess to hold the uric acid in solution. He determined the amount, reaction, urea, uric acid, acid phosphate, neutral phosphate, and sediment in twenty-five urines and came to the conclusion that the precipitation of uric acid is dependent on the relation between the amount of uric acid and the amount of neutral phosphate. If the ratio of the amount of uric acid to the amount of neutral phosphate present is greater than 0.35 or 0.40 to 1, there is a precipitate. If it is less, there is no precipitate. The acidity of the solution does not seem to influence the formation of a precipitate directly. He says that the solubility of the uric acid is dependent on the size of the uric acid production, on the amount of phosphate excreted, and the amount of acid in the organism, since this latter influences the relation between the acid and the neutral phosphates.

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[1] R. Höber. Ueber die Hydroxylionen des Blutes. Pflüger's Archiv, 81, 522 (1900).

[2] L. Rohrer. Die Bestimmung der Harnacidität auf elektrometrischem Wege. Pflüger's Archiv, 86, 586 (1901).

[3] Höber und Jankowsky. Die Acidität des Harns vom Standpunkt der Ionenlehre. Beiträge zur chemischen Physiologie und Pathologie, III, 525 (1903).

[4] Zerner. Ueber die chemischen Bedingungen für die Bildung von Harnsäure Sedimenten. Wien. klin. Wochenschrift, 6, 272 (1893).

Jahns [1] showed that .467 grams uric acid is soluble in one liter of a solution of alkaline sodium phosphate containing 1 gram of this salt. Calculating from the reaction $Na_2HPO_4.12\,H_2O + C_5H_4N_4O_3 = NaH_2PO_4 + NaC_5H_3N_4O_3 + 12\,H_2O$, we should expect one gram of Na_2HPO_4 to react with .469 grams of uric acid so that it seems probable that this equation represents the reaction that takes place. The fact that this reaction goes in the opposite direction in the urine when we obtain a precipitate of crystalline uric acid indicates that it is a reversible reaction. The equation $\frac{C_1C_2}{C_3C_4} = K$, in which C_1, C_2, C_3, and C_4 represent the concentrations respectively of the reacting substances Na_2HPO_4, $C_5H_4N_4O_3$, NaH_2PO_4, and $NaC_5H_3N_4O_3$, and K, a constant, determines whether the reaction written above takes place as indicated, from left to right, or in the reverse direction, from right to left. This equation $\frac{C_1C_2}{C_3C_4} = K$ is merely an expression of the mass action law of Guldberg and Waage. K is a constant, which can be calculated from the dissociation constants of the four electrolytes present. These dissociation constants are dependent merely on the compound itself, the temperature of the solution, and can be determined by experiment. In the last instance, therefore, since the dissociation constants determine the amount of dissociation of the electrolytes, the direction in which the reaction takes place depends on the relative concentration of the reacting substances and upon their relative dissociation. The dissociation of any one of them depends on the temperature, upon the concentration of each of the others, and also on the concentration from some other source of the ions into which it dissociates. Sodium chloride, for instance, which serves as a source of sodium ions, can influence the dissociation of sodium acid urate, which also dissociates in solution and gives sodium ions. K may have such a value that the reaction takes place in both directions until finally an equilibrium is reached in which some of all the reacting substances are present.

Smale [2] found that uric acid is soluble in a solution of the urinary salts of average composition to the extent of .63 grams in the

[1] Jahns. Ueber die Löslichkeit der Harnsäure in Salzlösung. Arch. f. Pharmacie, 221, 511 (1882).

[2] F. Smale. Beiträge zur Kenntniss der Lösungsbedingungen der Harnsäure im Harn. Maly's Jahresb. über die Fortschritte der Thierchemie, 25, 239 (1895).

daily amount of urine. Since the quantitative composition of the urine in salts is very variable, variable enough to make a considerable difference is its dissolving power for uric acid, Smale's work can be of little value.

Strauss [1] found that administration of calcium carbonate increased the solvent power of urine for uric acid. He found likewise that calcium carbonate decreased the amount of sodium acid phosphate in the urine without influencing the amount of sodium alkaline phosphate. To this increase in the ratio $\frac{Na_2HPO_4}{NaH_2PO_4}$ he attributed the increased solubility of the uric acid. Posner [2] and Lehmann [3] had previously found that administration of calcium carbonate gave the urine a greater solvent power for uric acid. The work of Posner, Lehmann, and Strauss is open to criticism and their conclusions thrown into great doubt on account of the fact that the methods used in their work were of doubtful accuracy.

Mordhorst [4] found that the sodium acid urate decomposes in distilled water, giving uric acid. This decomposition is slower in a solution of sodium chloride and ceases in a solution containing alkaline disodium phosphate. Acid hastens the decomposition. In a neutral solution containing both alkaline, disodium phosphate and acid sodium dihydrogen phosphate, the decomposition is slow, for the sodium set free from the urate changes some of the acid sodium phosphate to alkaline sodium phosphate. Mordhorst says that the decomposition of the urate and precipitation of uric acid is hastened by high acidity, high value of the ratio $\frac{\text{uric acid}}{\text{urea}}$, low concentration of salts, especially sodium chloride, and by low concentration of coloring matter; he does not think that a urate sediment can come down in an alkaline urine.

As we have seen, His and Paul found the dissociation constant for uric acid very small, so small, in fact, that the concentration of the hydrogen ions in a saturated solution of uric acid is com-

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[1] J. Strauss. Ueber die Einwirkung des kohlensäuren Kalkes auf den menschlichen Stoffwechsel, ein Beitrag zur Therapie der harnsäuren Nierenkonkretionen nebst Bemerkungen über Alloxurkörperausscheidung. Zeitschr. für klin. Med., 31, 493 (1896).

[2] Posner. Zur Therapie der Harnsäureüberschusses. Zeitschr. für klin. Med., XVII (1890) (cited by Strauss).

[3] L. Lehmann. Zur Wirkung des Kohlensäuren Kalkes und der kohlensäuren Magnesia. Berl. klin. Wochenschrift, 19, 320 (1882).

[4] C. Mordhorst. Die Entstehung und Auflösung der Harnsäureverbindungen ausserhalb und innerhalb des menschlichen Körpers. Zeitschr. für klin. Med., 32, 65 (1897).

parable with the concentration of the hydrogen ions in pure water. This explains the decomposition of sodium acid urate by water, noticed by Mordhorst. In an aqueous solution of a salt of a very weak acid, some of the acid itself is formed. In the case of sodium urate the hydrogen ions from the water react with the negative uric acid ions from sodium acid urate until the equilibrium expressed by the equation $\frac{C_H \times C_U}{C_{HU}} = K$ is reached. C_{HU}, which we have used to indicate undissociated uric acid, is a small constant, and the equilibrium may require formation of more HU than can remain in solution. In this case the uric acid will precipitate. Acids, of course, hasten the precipitation and alkalies stop it.

At this point it might be well to speak of the work of Pfeiffer. In 1886 [1] he found that if a urine be poured through a filter covered with a layer of uric acid, more or less of the uric acid of the urine is given up to the filter. He stated that the uric acid exists in the urine in two forms: "free uric acid" — by which, however, he did not mean chemically free — and "combined" uric acid The "free" uric acid is that given up to the uric acid filter. A few years later [2] he came to the conclusion that the "free uric acid" is that which comes down crystalline in urine, and the "combined" uric acid that which appears as amorphous sediment. He believed that in the periods free from attacks gouty people have the uric acid to a very large extent in the "free" form, and that if the urine of a person be filtered through a uric acid filter and then on treatment with hydrochloric acid the filtrate does not give a precipitate of uric acid a certain diagnosis of gout can be made. He says that in the attacks of gout, the uric acid previously almost entirely "free" becomes almost entirely "combined." This last statement that in gout the uric acid is almost entirely free has been contradicted by Feliziani,[3] and further, this author and also Schetelig [4] have found plenty of "free"

[1] E. Pfeiffer. Zur Aetiologie und Therapie der harnsäuren Steine. Verhandl. des 5t Kongr. für innere Medizin, Wiesbaden, 1886, 444.

[2] *Ibid.* Die Natur und Behandlung der Gicht. Verhandl. des 8t Kongr. für innere Medizin, Wiesbaden, 1889, 166.

[3] E. Feliziani. Sul valore della precipitabilita dell' acido urico, determinato col metodo di Pfeiffer nella diagnosi della Gotta. Rivista gener. ital. di chim. med., Pisa, 1890, 2, 360. Also Revue des Sciences Med., 1890, 460.

[4] A. Schetelig. Discussion of E. Pfeiffer's article, Die Natur und Behandlung der Gicht. Verhandl. des 8t Kongr. für innere Medizin 1889, 212.

uric acid in urine of healthy persons and others who have not gout.

Posner and Goldenberg,[1] and Roberts [2] found that the amount of uric acid given up to the filter is dependent on a number of circumstances, such as rapidity of filtration, acidity, and so forth. Rosenfeld [3] found that some of the uric acid is given up even to the filter paper.

Ritter [4] prepared a solution of phosphoric acid containing a known amount of P_2O_5 and a solution of disodium phosphate containing the same amount of P_2O_5. By mixing these two solutions in different proportions, he could obtain solutions containing any proportions of alkaline sodium phosphate and acid sodium phosphate. He also prepared solutions containing known quantities of sodium acid urate and urea. By mixing the four solutions he could simulate the conditions occurring in different urines.

In the presence of disodium hydrogen phosphate, Na_2HPO_4, the uric acid set free from the acid urate by sodium acid phosphate, NaH_2PO_4, is kept in solution. Since, however, the alkaline sodium phosphate, Na_2HPO_4, dissolves only that uric acid set free from the urate and does not help dissolve the sodium acid urate itself, Zerner was wrong in believing that the solubility of uric acid in the urine is dependent wholly on the ratio of the uric acid to the Na_2HPO_4.

Up to a certain concentration of Na_2HPO_4, Ritter showed that uric acid crystals can precipitate. Over that concentration, crystalline uric acid cannot precipitate. The concentration of the uric acid seems to influence only the rate of precipitation.

Another action of the Na_2HPO_4 is to increase the concentration of the Na ions, and thus to decrease the solubility of the sodium acid urate. This explains the formation of urate sediment in alkaline urine. Na_2HPO_4, as well as sodium bicarbonate, acetate, nitrate, sulphate, and so forth, gives a white precipitate of "kugel" urates. This shows that there is no formation of a double salt of phosphate and urate of sodium.

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[1] Posner und Goldenberg. Zur Auflösung harnsäurer Konkretionen. Zeitschr. für klin. Med., 13, 580 (1887).

[2] W. Roberts. Ueber Pfeiffer's Probe für latente Gicht. Maly's Jahresb. über die Fortschritte der Thierchemie, 21, 403 (1891).

[3] Rosenfeld und Orgler. Zur Behandlung der harnsäuren Diathese. Centralbl. für innere Medizin, 17, 42 (1896).

[4] A. Ritter. Ueber die Bedingungen für die Entstehung harnsäuren Sedimente, ein Beitrag zur Theorie der Gicht. Zeitschr. für Biologie, 35, 155 (1897).

In the case of formation of crystalline uric acid sediment there is either an entire absence of, or only very little, disodium phosphate. The acidity may be either high or low. The acid strength determines only the rapidity of precipitation.

Many urines give a precipitation of uric acid only after a very long time. This precipitation may be due to a gradual change of Na_2HPO_4 to NaH_2PO_4 by bacteria or some other process.

Ritter likewise explained the results obtained by Pfeiffer with the uric acid filter. If we take two equal portions of the same urine, to one add .3–.5 grams of uric acid, allow them to stand a few hours and then filter through a uric acid filter, the filtrate of the portion to which uric acid has been added contains less uric acid than the other. Part of the uric acid added is dissolved by alkaline sodium phosphate, forming sodium acid urate, and the alkaline phosphate changes to acid sodium phosphate. Then the undissolved uric acid causes a large part of the uric acid in solution to crystallize out. The explanation of the large amount of " free " uric acid found by Pfeiffer in the urine of those inclined to gout is that such urine probably contains only a small amount of alkaline phosphates. The filtrate from a urine passed through a uric acid filter may contain the same, or more, or less, uric acid than before it is filtered. The result is dependent on the velocity of filtration, the acidity of the urine, the concentration of uric acid, the temperature, the height of uric acid layer, and so forth.

At the congress for internal medicine at Wiesbaden in 1902, Klemperer [1] read a paper in which he stated that the uric acid in the urine exists chiefly in the form of a salt and as free uric acid in the colloidal form, and that there was usually rather more of the free acid than the salt. He determined the total uric acid in a quantity of urine by the Ludwig-Salkowski method, and then after shaking the same quantity of urine with crystalline uric acid for a couple of days, he filtered and determined the uric acid in the filtrate. He assumed that shaking with crystalline uric acid would precipitate colloidal uric acid and only colloidal uric acid. The uric acid in the filtrate then would be that present as urate and the difference between this value and the total would be the uric acid in the colloidal form. He further attempted to show that urochrome is the agent which keeps uric acid colloidal

[1] G. Klemperer. Untersuchungen über die Lösungsverhältnisse der Harnsäure im Urin. Verhandl. des 20t Kongr. für innere Medizin, Wiesbaden, 1902, 219.

in the urine. McCrudden [1] showed that Klemperer's work was open to criticism from a number of points, that he had merely done in a slightly different way what Pfeiffer [2] had done with his uric acid filter, and that his results were of no value, since the explanation that Ritter [3] gave of Pfeiffer's results applies equally well to Klemperer's.

Singer,[4] too, has recently spent some time in studying the effect of foods and drugs on the relative quantities of free and combined uric acid in the urine.

It seems probable from the work of Klemperer [5] and also from that of Roberts [6] and Herter [7] that urochrome may be one of the agents which retard the precipitation of uric acid when the urine cools.

An explanation of the behavior of uric acid in the urine is offered if we turn to physical chemistry for assistance.[8] The affinity constant K in the equation $\frac{C_H \times C_U}{C_{HU}} = K$ is .00000151 according to His and Paul.[9] (C_H stands for the concentration of the hydrogen ions, C_U for the concentration of the negative uric acid ions, and C_{HU} for the undissociated uric acid.) C_{HU} is a constant, equal, at 18°, to .0001363.[9] Then $\frac{C_H \times C_U}{.0001363} = .00000151$, or the solubility product $C_H \times C_U = .00000151 \times .0001363 = 206 \times 10^{-12}$ (I). In the 1,500 cc. of urine daily excreted, there is on the average .75 gram uric

[1] F. McCrudden. A Criticism of Klemperer's Work on the Condition of Uric Acid in the Urine. Boston Medical and Surgical Journal, August, 1903.

[2] E. Pfeiffer. Zur Aetiologie und Therapie der harnsäuren Steine. Verhandl. des 5t Kongr. für innere Medizin, Wiesbaden, 1886, 444.

Ibid. Die Natur und Behandlung der Gicht. Verhandl. des 8t Kongr. für innere Medizin, Wiesbaden, 1889, 166.

[3] A. Ritter. Ueber die Bedingungen für die Entstehung harnsäurer Sedimente, ein Beitrag zur Theorie der Gicht. Zeitschr. für Biol., 35, 155 (1897).

[4] H. Singer. Beiträge zur Lösungsfähigkeit des Harns für die Harnsäure. Dtsch. Aerzte Zeitung, 1903, 505.

[5] G. Klemperer. Untersuchungen über die Lösungsverhältnisse der Harnsäure im Urine. Verhandl. des 20t Kongr. für innere Medizin, Wiesbaden, 1902, 219.

[6] W. Roberts. Chemistry and Therapeutics of Uric Acid Gravel and Gout. (Croonian Lectures.) Lancet, 1902.

[7] C. A. Herter. Some Practical Points Regarding the Excessive Excretion of Uric Acid. New York Medical Journal, 58, 8 (1893).

[8] See also F. McCrudden. The Application of Physical Chemistry to the Study of Uric Acid in the Urine. Read at the Meeting of the Am. Ass. for the Advancement of Science, St. Louis, December 28, 1903, and Journal of the Am. Chem. Soc., March, 1904.

[9] W. His und T. Paul. Physikalisch-chemische Untersuchungen über das Verhalten der Harnsäure und ihrer Salze in Lösungen. I. Abhandlung. Zeitschr. für physiol. Chem., 31, 1 (1900).

acid excreted in the form of sodium acid urate. This is .5 gram per liter, or, dividing by the molecular weight, about .003 gram molecules per liter. A salt in such dilute solution is almost completely dissociated, so that in an aqueous solution of sodium acid urate, of the concentration found in the urine, C_U, in equation I, becomes .003. Then $C_H \times .003 = 206 \times 10^{-12}$ or $C_H = \frac{206 \times 10^{-12}}{.003} = 7. \times 10^{-8}$. If 2 grams per day uric acid were excreted, a rather high limit, C_H would be about 2×10^{-8}. If only .1 gram uric acid were excreted per day with the ordinary amount of urine, or if in a diseased condition the amount of urine should increase to 4 liters, and only .4 gram uric acid were excreted, C_H would increase to 34×10^{-8}. In other words, in an aqueous solution of sodium urate of the concentration of average urine, we can have hydrogen ions present in a concentration of only about $7. \times 10^{-8}$ without a precipitation of uric acid. With the ordinary variations in the amount of urate present in urine, the figure would vary from about 4×10^{-8} to 15×10^{-8}. In extreme pathological cases it might vary from 2×10^{-8} to 35×10^{-8}. If the concentration of the hydrogen ions increases beyond the limit set by the equation $C_H \times C_U = 206 \times 10^{-12}$, then undissociated uric acid will form, and precipitation of uric acid will occur.

The average acidity of urine, expressed by the concentration of the hydrogen ions, is 300×10^{-8} according to Rhorer,[1] and 150×10^{-8} according to Höber and Jankowsky.[2] Rhorer found the value to vary in different urines from 40×10^{-8} to 610×10^{-8}. Höber and Jankowsky obtained results varying from 100×10^{-8} to $1{,}000 \times 10^{-8}$. In a very few pathological cases the value was slightly outside these limits. We can see, then, why uric acid should precipitate from cold urine. The concentration of the hydrogen ions is too great to permit the presence of the large quantity of negative uric acid ions present, so precipitation of uric acid occurs. The fact that uric acid does not always precipitate immediately from the cold urine is due, as His [3] has shown,

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[1] L. Rhorer. Die Bestimmung der Harnacidität auf elektrometrischen Wege. Pflüger's Archiv, 86, 586 (1901).

[2] Höber und Jankowsky. Die Acidität des Harns vom Standpunkt der Ionenlehre. Beiträge zur chemischen Physiologie und Pathologie, III, 525 (1903).

[3] W. His. Die Harnsäureablagerung des Körpers und die Mittel zu ihrer Lösung Therapie des Gegenwart, Neue Folge, 3, 434 (1901).

to the fact that the insoluble uric acid goes into the colloidal condition and does not precipitate for some time. Even when hydrochloric acid is added to the solution, some of this insoluble uric acid is not precipitated for weeks. As Pfeiffer,[1] His,[2] and Klemperer[3] have shown, this colloidal uric acid can be precipitated by thoroughly shaking the solution with uric acid.

Klemperer showed that when urine is thoroughly shaken with solid uric acid, a variable part, but not the whole, of the uric acid present is precipitated from solution. An explanation of this fact is easily given. The acidity of the urine as determined by titration (that is, "potential acidity"), is about ten thousand times as great as the real acidity. We have seen that as soon as the "actual" hydrogen ions present are used up by titration with alkali, more of the "potential" hydrogen ions are set free to preserve the equilibrium indicated by the equation $\frac{C_H \times C_A}{C_{HA}} = K$, where C_{HA} is used to indicate the acid or acid bodies to which urine owes its acidity, — probably chiefly NaH_2PO_4. The same thing occurs when the "actual" H ions are carried out of solution by precipitation as uric acid. If merely enough uric acid disappears from solution to use up the actual hydrogen ions present, the actual acidity of the solution remains practically unaffected, for immediately more H ions are set free from the undissociated HA until equilibrium is reached. In the equation $\frac{C_H \times C_{HPO_4}}{C_{H_2PO_4}} = K$, we know that K is small, that is, $C_{H_2PO_4}$ is large in comparison with C_H and C_{HPO_4}. Then for small changes in $C_{H_2PO_4}$ due to setting free of H and HPO_4 to establish equilibrium after disappearance of H on account of precipitation of uric acid, we can consider $C_{H_2PO_4}$ constant practically. We know that on account of the presence of Na_2HPO_4, largely dissociated to Na_2 and HPO_4, C_{HPO_4} is large in comparison with C_H, so that for small changes in C_{HPO_4}, due to the further dissociation of H_2PO_4 to establish equilibrium after disappearance of the "actual" H ions, C_{HPO_4} may be considered practically constant. If we

[1] E. Pfeiffer. Zur Aetiologie und Therapie der harnsäuren Steine. Verhandl. des 5t Kongr. für innere Medizin, Wiesbaden, 1886, 444.

[2] W. His. Die Harnsäureablagerung des Körpers und die Mittel zu ihrer Lösung. Therapie des Gegenwart, Neue Folge, 3, 434 (1901).

[3] G. Klemperer. Untersuchungen über die Lösungsverhältnisse der Harnsäure im Urine. Verhandl. des 20t Kongr. für innere Medizin, Wiesbaden, 1902, 219.

consider $\frac{C'_H \times C'_{HPO_4}}{C'_{H_2PO_4}} = K$ the initial equation, then after precipitation of a very little uric acid we have the new equation $\frac{C''_H \times C''_{HPO_4}}{C''_{H_2PO_4}} = K$, where $C''_{HPO_4} = C'_{HPO_4}$, approximately, and $C''_{H_2PO_4} = C'_{H_2PO_4}$, approximately. Therefore C_H is approximately constant. In other words, after a small amount of uric acid has precipitated, the concentration of the H ions is almost the same as before, so that the solubility constant for uric acid is still exceeded, and more uric acid precipitates. But, as uric acid precipitates in larger amounts, the loss of H ions from the H_2PO_4 will decrease the value for $C_{H_2PO_4}$, and the HPO_4 ions formed at the same time will increase the value for C_{HPO_4} in the equation. Then C_H must decrease in order to maintain equilibrium. Obviously a time will come when this decrease in H ions and the decrease in negative U ions brought about through loss of uric acid by precipitation will be so great that $C_H \times C_U$ will be less than 206×10^{-12}. Then no more uric acid will precipitate.

Let us take the value for normal urine $C_H = 150 \times 10^{-8}$, and the amount of uric acid excreted as .75 grams in 1,500 cc. urine. Then $C_U = .003$. Let us suppose that by spontaneous precipitation of uric acid, or by addition of alkali, C_H has decreased to 15×10^{-8}, or to $\frac{1}{10}$, its initial value, then $C_H \times C_U = 206 \times 10^{-12}$ becomes $15 \times 10^{-8} \times C_U = 206 \times 10^{-12}$ and $C_U = \frac{206 \times 10^{-12}}{15 \times 10^{-8}} = 15 \times 10^{-4} = .0015$. In this case equilibrium is reached when the acidity of the urine has been decreased to $\frac{1}{10}$ of its initial value and $\frac{1}{2}$ the uric acid has precipitated.

Ritter,[1] it will be remembered, found that the equilibrium is reached more quickly, that is, less uric acid is precipitated when large quantities of Na_2HPO_4 are present than when small quantities of Na_2HPO_4 are present. This is easy to understand. The addition of Na_2HPO_4 means the addition of HPO_4 ions. The formation of H_2PO_4 by the union of even a large part of the H ions present with HPO_4 would scarcely affect the total value for $C_{H_2PO_4}$, since $C_{H_2PO_4}$ is so large in comparison with C_H. From the equation $C_H \times C_{HPO_4} = K \times C_{H_2PO_4}$ (a constant in this case), we can see that the addition of HPO_4 will decrease C_H in

[1] A. Ritter. Ueber die Bedingungen für die Entstehung harnsäurer Sedimente, ein Beitrag zur Theorie der Gicht. Zeitschr. für Biologie, 35, 155 (1897).

the same ratio as C_{HPO_4} increases. Further, we know that Na_2HPO_4 is alkaline. That is, a solution of Na_2HPO_4 contains OH ions. (This is due to the fact that the reaction $Na_2^{++} + HPO_4^{--} + H^+ + OH^- = Na_2^{++} + H_2PO_4^- + OH^-$ takes place to some extent.) On addition of a solution of Na_2HPO_4 to one of NaH_2PO_4, the reaction of $H^+ + OH^- = HOH$ takes place, thus still further decreasing the concentration of the H ions. Therefore the value of C_H in the equation $C_H \times C_U = 206 \times 10^{-12}$ will be reached sooner when Na_2HPO_4 is added to the solution, and will necessitate the precipitation of a smaller quantity of uric acid before equilibrium is reached.

The effect of a small addition of alkali to a cold urine would be the same as the effect of a slight precipitation of the uric acid. The hydroxyl ions from the alkali would combine with the "actual" H ions, in order that the value $C_H \times C_{OH} = .64 \times 10^{-14}$ should not be exceeded. But then, just as the precipitation of a little uric acid by carrying away the actual hydrogen affects the values in the equation $\frac{C_H \times C_{HPO_4}}{C_{H_2PO_4}} = K$ very little, so the value of C_H would not be affected by the addition of a little alkali. Therefore, since $C_H \times C_U =$ a constant, and the addition of a little alkali does not change C_H, C_U is not changed, so that the addition of a little alkali does not change the solubility of uric acid in cold urine. It has, in fact, been shown by experiment, as we shall see later, that partial neutralization of the acidity of a cold urine by alkali does not give it the power of dissolving uric acid crystals. When, however, enough alkali is added to very decidedly decrease $C_{H_2PO_4}$, and correspondingly increase C_{HPO_4}. C_H is decreased to maintain equilibrium, and when C_H is decreased enough to approach the concentration allowed by the equation $C_H \times C_U = 206 \times 10^{-12}$, then the solubility of uric acid begins to be increased.

With increase in temperature, K generally increases. C_{HU}, the value for the solubility of the undissociated uric acid, also increases. Therefore, $C_H \times C_U = K \times C_{HU}$ is very largely increased, and since C_U is a constant for any given urine, the value $C_H = \frac{K \times C_{HU}}{C_U}$ is greatly increased. In other words, the concentration of the H ions, which can exist in solution with a definite amount of negative urate ions, is increased with the

temperature. With increase in temperature, there is also an increase in the dissociation of the other weak bases and acids in the urine. But the OH ions from the bases neutralize the H ions from the acids, according to the equation $H \times OH = HOH$. If the increase in the supply of the OH ions is equal to the increase in the supply of the H ions on warming, the actual concentration of H ions will remain the same with increase in temperature. In the equation $C_H \times C_U = K \times C_{HU}$ or $C_U = \frac{K \times C_{HU}}{C_H}$ we have, in such a case, K increasing, C_{HU} increasing, and C_H constant. Therefore, C_U must increase. That is, the amount of negative uric acid ions or sodium urate that can remain in solution is greater. Or, to put it more generally, if the increase in concentration of OH ions is rapid enough to prevent the actual concentration of the H ions in any urine from increasing as rapidly as the value for C_H in the equation $C_H = \frac{K \times C_{HU}}{C_U}$, then the solubility of the uric acid will increase with increase in temperature. If the concentration of the OH ions increases faster than the concentration of the H ions, the actual value for the concentration of the H ions will decrease with increase in temperature. In this case, which, as we shall see, is probably the condition in normal urine, the solubility of the uric acid will increase with rise in temperature faster than it will increase in pure water. As the value C'_H for the actual concentration of H ions decreases, and the value C''_H for the concentration of H ions permitted by the equation $C_H = \frac{K \times C_{HU}}{C_U}$ increases, a point will be reached where $C'_H = C''_H$. As we pass this point, uric acid becomes the strongest acid in the urine, and, in fact, we have proof that at 37° uric acid is the strongest acid in the urine.

Tunicliffe and Rosenheim[1] took a set of flasks containing 100 cc. of urine each, and containing an excess of undissolved uric acid, added to each .2 gram of different alkalies, and allowed the solutions to remain at a temperature of about 37° until saturated. The alkalies used were piperidine, lysidin, and piperazin. These authors found that the amount of uric acid dissolved by each was proportional to the solubility of their respective

[1] F. Tunicliffe and O. Rosenheim. Piperidine as a Uric Acid Solvent, a Comparative Study. Lancet, July 23, 1898.

urates. If there were a stronger acid than uric acid present, we should have the condition described on page 85, that is, these alkalies would not affect the solubility of the uric acid. On addition of a little alkali, the H ions would disappear to form HOH. Immediately new H ions would be supplied by dissociation of the stronger acid HA. In the case of warm urine, however, as the H ions disappear, more are supplied by further dissociation of HU. But this decreases the concentration of the undissociated HU. Therefore more uric acid goes into solution to supply this deficiency.

The precipitation of sodium acid urate takes place when the value $C_{Na} \times C_U$ exceeds the constant $K \times C_{NaU}$, where C_{NaU} is the value for the solubility of undissociated sodium acid urate. ($C_{Na} \times C_U = K \times C_{NaU}$). Therefore, either a high concentration of sodium salts or a large amount of uric acid might bring about a precipitation of sodium urate. We can see a reason, therefore, for a precipitation of the urate in alkaline urine, a condition which sometimes occurs. A precipitation of both uric acid and sodium acid urate, such as we often have in urine, will occur when the concentration of Na ions, H ions, and negative U ions is such that the values for the solubility products of both the uric acid and the sodium urate are exceeded.

What now will be the effect of alkali on a urine from which uric acid precipitates while still warm? Obviously, in this case, the solubility product $C_H \times C_U = K$ is exceeded even in the warm urine. Therefore uric acid is not the strongest acid in solution. We have in this case the condition usually found in cold urine. The addition of a little alkali will not, therefore, affect the solubility of the uric acid. Addition of large amounts of alkali will have some effect on the solubility of the uric acid.

By the addition, then, of alkali to a normal urine, we should increase the solubility of uric acid in it at the body temperature, and by the addition of considerable quantities of alkali to a urine from which uric acid precipitates while still warm, we should expect to increase its power of dissolving uric acid at the body temperature. As it is the latter case with which we have to deal in practical therapeutics, we should for the best results give as much alkali as it is possible to give without making the urine alkaline.

We hope to determine the dissociation constants

$K_1 = \frac{C_H \times C_{HPO_4}}{C_{H_2PO_4}}$ (at 18°), $K_2 = \frac{C_H \times C_{HPO_4}}{C_{H_2PO_4}}$ (at 37°), $K_3 = \frac{C_H \times C_U}{C_{HU}}$ at 37°), and to study the "actual" and "potential" acidity of different urines at 18° and at 37°, their content of alkaline and acid sodium phosphate, and uric acid, and the amount of uric acid precipitated on cooling, in order that the conditions in urine be made still clearer, and that we may be able to predict quantitatively the effect of a certain amount of alkali on a urine and the amount of uric acid which will precipitate spontaneously on cooling from the chemical composition and acidity of the urine.

There is no reason to believe that the precipitation of the acid urate of sodium or ammonium is anything more than a simple precipitation due to decreased solubility in the cool urine. Of course, the absence of conditions which change the urate to uric acid influence the precipitation. A large amount of urate, a large amount of sodium salts which decrease the dissociation and therefore the solubility of the urate of sodium, and small amount of urine, tend to bring about a precipitation of urate. We may have, too, a mixed precipitate of urate and uric acid.

Uric Acid in the Blood and Tissue Fluids

Garrod[1] found a small amount of uric acid in the watery extract of evaporated human blood by precipitation with hydrochloric acid. Abeles[2] found it in blood by means of the murexid test. Pétren[3] thinks it is normally in the blood. Neither v. Jaksch[4] nor Klemperer[5] could find uric acid in normal human blood.

Uric acid has been found in the blood in different diseases. Garrod[6] has found it in gout, Klemperer[7] and Magnus-Levy[8] in leukemia and nephritis, v. Jaksch[4] in typhus, malaria, carcinoma of the liver, heart diseases, and diseases of the lungs and

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[1] Garrod. Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism, and Bright's Disease. Med. Chir. Trans., Bd. XXXI, 83, 1848.

[2] Abeles. From Schreiber. Ueber Harnsäure. Stuttgart, 1899, p. 26.

[3] Pétren. From Schreiber. Ueber die Harnsäure. Stuttgart, 1899, p. 26.

[4] R. v. Jaksch. Ueber Uricacidämie. Deutsche Med. Wochenschrift, 16, 33 (1890).

[5] Klemperer. Untersuchungen über Gicht und harnsäure Nierensteine. Berl., 96, 3.

[6] Garrod. The Nature and Treatment of Gout.

[7] Klemperer. Gicht, 3.

[8] A. Magnus-Levy. Ueber den Stoffwechsel bei acuter und chronischer Leukämie. Virchow's Archiv, 152, 107 (1898).

pleura. Salomon [1] and Pétren [2] have found it in the blood in pneumonia and anæmia. Pétren [2] has found it in the blood in a case of hysterical vomiting and in a case of gonorrheal rheumatism. In anæmia, Boucheron [3] has found uric acid in the saliva and in the mucus of the nose, pharynx, bronchi, uterus, vagina, stomach, and fluids of the eye. Colosanti [4] found it in the vomitus in a case of hysterical oligurea.

It has been found by v. Jaksch [5] and by Pickardt [6] in transudates and exudates, especially in nephritis, and by Naunyn [7] in pleuritic and other fluid exudates. We have, of course, the uric acid concretions in gout, the uric acid stones, and the uric acid infarcts in addition.

Cloetta [8] found uric acid in the human spleen, lungs, liver, and brain, and Abeles [9] in the human spleen, liver, cartilage, and connective tissue. Abeles found in the liver and muscles of dogs and horses, likewise, a very small trace of uric acid, but found none in their blood. Meissner [10] found it in the blood of dogs, but Lütze [11] could not find it. v. Jaksch,[5] Schröder,[12] Pétren,[2] could not find it in the blood of rabbits, rams, cattle, swine, or horses. Garrod,[13] too, could not find it in rams' blood. Nencki and Kowarski [14] could find no uric acid in the muscles of mammals.

We do not know at the present time in what condition the uric

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[1] G. Salomon. Ueber die Verbreitung und Entstehung von Hypoxanthin und Milchsäure im thierischen Organismus. Zeitschr. für physiol. Chem., 2, 65 (1878).

[2] K. Pétren. Ueber das Vorkommen von Harnsäure im Blute bei Menschen und Säugethiere. Arch. für exp. Path. u. Pharm., 41, 265 (1898).

[3] Boucheron. De l'acide urique dans la salive et dans de mucus nasal pharinge, bronchique, utero-vaginal. Comptes rendus, 100, 1308.

[4] G. Colosanti. Ueber das Erbrechen bei Oligurie. Moleschott's Unters. z. Naturlehre d. Menschen., 14, Separatabde, 10 p.

[5] v. Jaksch. Ueber Uricacidämie. Deutsche Med. Wochenschrift, 16, 33 (1890).

[6] M. Pickardt. Zur Kenntniss der Chemie pathologischer Ergüsse. Berl. klin. Wochenschrift, 34, 39 (1897).

[7] Naunyn. Arch. für Anat. u. Physiol., 1864, 188.

[8] A. Cloetta. Ueber das Vorkommen von Inosit, Harnsäure, etc., in thierischen Körper. Liebig's Ann. der Chem. u. Pharm., 99, 289 (1856).

[9] Abeles. From Schreiber. Ueber Harnsäure., Stuttgart, 1899, p. 26.

[10] G. Meissner. Beiträge zur Kenntniss des Stoffwechsels im thierischen Organismus. Zeitschr. für rat. Med., III, 31, 144 (1868).

[11] Lütze (from Klemperer, Gicht).

[12] W. v. Schröder. Ueber den Harnsäuregehalt des Blutes und der Leber der Vögel. C. Ludwig'sche Festschrift, Leipzig, 1887.

[13] Garrod (see Pétren). Ueber das Vorkommen von Harnsäure im Blute bei Menschen und Säugethiere. Arch. für exp. Path. u. Pharm., 41, 265 (1898).

[14] Nencki und Kowarski. Ueber das Vorkommen von Harnstoff im Muskel der Säugethiere. Arch. für exp. Path. u. Pharm., 36, 395 (1895).

acid exists in the blood. Wittich[1] stated that it is not found free, but as a salt, and probably the neutral urate, since this is the most soluble of the common urates. Carbon dioxide will precipitate the less soluble acid urate from a solution of neutral urate. The carbon dioxide in the tissues may cause the acid urate to precipitate from the blood in this way in gout, according to Wittich.[1] Again, the tissues may withdraw some of the base from the neutral urate, forming thereby alkali albuminate, and leaving the insoluble acid urate. Pawlinoff[2] thinks that the hypotheses of Wittich may be correct.

The views of Wittich and Pawlinoff do not seem to have been questioned until Roberts[3] called attention to the fact that neutral sodium urate cannot exist in a solution that contains no free sodium hydroxide, and that it cannot exist in a solution containing carbonic acid. Neutral sodium urate then can certainly not exist in the blood.

The view of Roberts that uric acid circulates in the blood as sodium quadriurate is an hypothesis based simply on the fact that Roberts and Jones believed that quadriurates exist. It has been shown, however, that there is no reason to believe that such compounds exist.

We have seen that it has not been possible to prepare a double compound of sodium acid urate and alkaline sodium phosphate. Hence the view of Pfeiffer[4] that the uric acid circulates in the blood in the form of a double salt of acid urate and alkaline phosphate of sodium has no foundation in fact.

Mordhorst[5] believed that the uric acid is not dissolved in the blood, but is suspended in a finely divided condition loosely combined with varying amounts of sodium. This is the condition of the so-called "kugel" urates, according to him. Mordhorst's theory is, however, based on a fallacy. It has been shown that the "kugel" urates, are definite chemical compounds. His later

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[1] v. Wittich. Ueber Harnsecretion und Albuminurie. Virchow's Archiv für Path. Anat., 10, 325 (1856).

[2] C. Pawlinoff. Die Bildungsstätte der Harnsäure im Organismus. Virchow's Archiv für Path. Anat., 62, 57 (1875).

[3] W. Roberts. On the Chemistry and Therapeutics of Acid Uric Gravel and Gout. (Croonian Lecture for 1892.) Lancet, 1892.

[4] E. Pfeiffer. Ueber Harnsäureverbindungen beim Menschen. Berl. klin. Wochenschrift, 31, 913 (1894).

[5] C. Mordhorst. Die Entstehung und Auflösung der Harnsäureverbindungen ausserhalb und innerhalb des menschlichen Körpers. Zeitschr. für klin. Med., 32, 65 (1897).

view,[1] that the "kugel" urates are compounds of sodium hydroxide and uric acid, are, as we have seen, erroneous.

We have no reason to believe that the uric acid exists in the blood and tissues in the form of a salt. Until recently it has been very generally believed that uric acid is destroyed in the organism, and cannot exist in the blood. To explain the presence of uric acid in the urine under these circumstances, von Noorden offered the suggestion that the uric acid might be united in some organic compound in some such way that it was not capable of being oxidized to urea, and that uric acid is set free only in the kidneys. Goto[2] has prepared soluble compounds of uric acid with nucleic acid and thymic acid from which the uric acid is not precipitated by hydrochloric acid or the other common uric acid precipitants. Minkowski,[3] in a discussion of one of His's articles, stated that he had prepared the same compounds. His[4] has prepared a similar compound of uric acid and formaldehyde, and he thinks that there are undoubtedly a large number of bodies which combine organically in this way with uric acid. If, as His suggests, the uric acid in the body is combined not as a salt, but organically, in some such way as with thymic acid, it may be present in much higher concentration than we suspect, for our usual tests do not show its existence when it is combined in this way. Schmoll,[5] too, has suggested that uric acid circulates in the blood in combination with thymic acid, but has not offered any good evidence for his view.

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[1] C. Mordhorst. Wirkungsweise des kohlensäuren und des salicylsauren Natrons bei Gicht, Rheumatismus, etc. Centralbl. für innere Medizin, 18, 409 (1898).

[2] M. Goto. Ueber die Lösung der Harnsäure durch Nucleinsäure und Thyminsäure. Zeitschr. für physiol. Chem., 30, 473 (1900).

[3] Minkowski's discussion of His's article. W. His. Das Verhalten des Harnsäure im thierischen Organismus. Verhandl. des 17t Kongr. für innere Medizin, Wiesbaden, 315 (1899).

[4] W. His. Schicksal und Wirkungen des säuren harnsäuren Natrons in Bauch und Gelenkhöhle des Kaninchens. Deutsche Archiv für klin. Medizin, 67, 81 (1900).

[5] E. Schmoll. Sur la Formation de l'acide urique dans la goutte et les causes de sa précipitation dans les tissus. Arch. gén. de Med., 2, 2433 (1904).

II. Physiology of Uric Acid

Uric Acid in Birds

A study of the nitrogenous metabolism of birds is of considerable importance for a correct understanding of the metabolism of uric acid in mammals. Although it has been shown that uric acid in birds is analogous to urea in mammals in that it is the chief end product of their nitrogenous metabolism, yet Wiener,[1] as a result of his work on the subject, seems to think that the formation of uric acid in birds and in mammals takes place in the same way, and that the difference lies in the relative quantities formed by each method in the two classes of animals. There is some objection to this theory, however, as we shall see later.

In birds, and in certain reptiles, the chief end product of nitrogenous metabolism is uric acid. It is formed by oxidation of proteid, and a generation or so ago — and even more recently — the uric acid in mammals was very generally supposed by analogy to come from proteid. Since outside the body urea can be obtained by oxidation of uric acid, the formation of uric acid in mammals was supposed to be due to incomplete oxidation of proteid. All theory and experiment upon the subject was based upon this view, which we know now to be incorrect.

Uric acid was first found in the excrement of birds by Fourcroy and Vauquelin,[2] and in that of serpents by Prout.[3] Wollaston [4] found calcium urate and uric acid in the urine of different birds. v. Wittich[5] showed that uric acid concretions were formed in the epithelium cells of the kidney, and excretion took

[1] H. Wiener. Ueber synthetische Bildung der Harnsäure im Tierkörper. Verhandl. des 19t Kongr. für innere Medizin, Wiesbaden, 383 (1901), and Beiträge zur chemisch. Physiol. u. Pathol., 242 (1902).

[2] Fourcroy and Vauquelin. Sur le guano, ou sur l'engrais naturel des îlots de la mer du Sud, près des côtes du Perou. Annales de Chimie, 56, 258 (1805).

[3] Thomson. Analysis of the Excrements of the Boa Constrictor. Annals of Philosophy, 5, 413 (1815).

[4] Wollaston. Annales de Chimie, 76, 31 (1810).

[5] v. Wittich. Harnsäuresecretion und Albuminurie. Virchow's Archiv, 10, 325 (1856).

place as these cells degenerated. Coïndet[1] and Davy[2] thought that the uric acid in bird excrement is combined as ammonium urate, and Cap and Henry[3] that it is combined with urea which Coïndet[1] had shown to exist in small quantities in the excrement. Meissner,[4] and later v. Knierem,[5] proved experimentally that the excrement consists chiefly of free uric acid and not of a compound of uric acid. Some urates were found. According to Milroy,[6] small amounts of purin bases are found in birds' urine.

The Nitrogenous Metabolism in Birds

Both Coïndet[1] and Zalesky[7] found urea in the excrement of birds, but Cech[8] found that if urea were administered to birds, it did not reappear in the urine. This was explained by Meyer and Jaffe,[9] by Cech,[8] and by Meyer.[10] These authors showed that the administration of urea to birds does not increase the excretion of urea, but does increase the excretion of uric acid. Further, according to v. Knierem,[11] amido acids which are sometimes obtained as decomposition products of proteid, and which, when administered to mammals, increase the excretion of urea, in birds are changed to uric acid. According to this author, ammonium salts do not change to uric acid in the organism of birds. v. Schröder[12] has shown, however, that only ammonium chloride

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[1] Coïndet. Considerations sur la production de l'acide urique. Bibliotheque universelle, T. XXX, p. 495. Geneva (1825).

[2] Davy. Physiological Researches, p. 191. London and Edinburgh (1863).

[3] Cap und Henry. Ueber milchsäuren Harnstoff, nebst Bemerkungen über Harnstoff und Milchsäure und ihre Salze überhaupt, so wie über den Zustand des Harnstoffs im Urine. J. de Pharm., 133 (1839).

[4] G. Meissner. Beiträge zur Kenntniss des Stoffwechsels im thierischen Organismus. Zeitschr. für rationelle Med., III Reihe, 31, 144 (1868).

[5] W. v. Knierem. Verhalten der im Säugethierkörper als Vorstufen des Harnstoffs erkannten Verbindungen zum Organismus der Hühner. Zeitschr. für Biol., 13, 36 (1877).

[6] T. Milroy. The Formation of Uric Acids in Birds. Journ. of Physiol., 30, 47 (1903).

[7] Zalesky. Untersuchungen über den urämischen Prozess und die Funktion der Nieren. Tübingen, 1865.

[8] C. O. Cech. Ueber das Verhalten des Taurins in Organismus der Vögel. Ber. der Dtsch. chem. Gesell., 10, 1461 (1877).

[9] H. Meyer und W. Jaffe. Entstehung der Harnsäure im Organismus der Vögel. Ber. der Dtsch. chem. Gesell, 10, 1930 (1877).

[10] H. Meyer. Beiträge zur Kenntniss des Stoffwechsels im Organismus der Hühner. Dissertation, Königsberg, 1877.

[11] W. v. Knierem. Verhalten der im Säugethierkörper als Vorstufen des Harnstoffs erkannten Verbindungen zum Organismus der Hühner. Zeitschr. für Biol., 13, 36 (1877).

[12] W. v. Schröder. Ueber die Verwandlung des Ammoniaks in Harnsäure im Organismus des Hühns. Zeitschr. für physiol. Chem., 2, 228 (1878).

and sulphate and those ammonium salts which are easily changed into the chloride of sulphate are excreted unchanged, and that ammonium carbonate and those salts of ammonia with organic acids which change to ammonium carbonate on oxidation are excreted as uric acid. This author expressed the view that in this case we have a synthesis of uric acid.

These experiments which showed that urea, ammonium compounds, and amido acids are changed to uric acid in birds seemed to indicate some analogy between uric acid in birds and urea in mammals. With the exception of the article of Fränkel and Röhmann,[1] who found that in hens suffering from phosphorus poisoning the excretion of uric acid is increased, and who think that this is due to defective oxidation of proteid, very little reference is made during the last twenty-five years to the formation of uric acid in birds as a process of defective oxidation. The analogy between the formation of urea in mammals and uric acid in birds was strongly confirmed by Cazeneuve,[2] who found that the relative amounts of urea, uric acid and ammonia excreted were the same whether the birds have an excessive or a deficient amount of oxygen, and that the absolute amounts of each were dependent upon the quantity of nitrogenous food taken. Further confirmation of this analogy was given by Schimanski,[3] who showed that like the urea in animals' urine, so the uric acid in birds' urine rapidly increases toward the end in inanition.

Organ of Formation of Uric Acid in Birds

Strahl and Lieberkühn[4] analyzed the blood of doves, hens, and snakes, and found it free from uric acid. He concluded, therefore, that the uric acid is formed in the kidneys. Zalesky[5] confirmed the discovery of Strahl and Lieberkühn. He found, also, that after tying the ureters of snakes, geese, and hens,

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[1] A. Fränkel und F. Röhmann. Phosphorvergiftung bei Hühnern. Zeitschr. für physiol. Chem., 4, 439 (1880).

[2] P. Cazeneuve. Sur l'excretion de l'acide urique chez les oiseaux. Compte rend. de sociét. biol., 93, 1155 (1881).

[3] H. Schimanski. Der Inanitions und Fieberstoffwechsel der Hühner. Zeitschr. für physiol. Chem., 3, 396 (1889).

[4] Strahl und Lieberkühn. Harnsäure im Blute und einige neue Bestandtheile des Urins. Berlin (1848). Also Jahresber, über die Fortschritte in die gesammten Medicin (1848).

[5] Zalesky. Untersuchungen über den urämischen Prozess und die Funktion der Nieren. Tübingen, 1865.

concretions of uric acid appear in the different organs of the animal. These concretions appear first in the kidneys and later in the other organs. When the kidneys are extirpated in snakes, or cut out of the circulation by tying off the blood supply in birds, the uric acid concretions do not appear, according to Zalesky. These facts seemed to indicate the kidneys as the organs in which uric acid is formed. Chrzonszczewsky[1] likewise found uric acid concretions in the various organs and tissues of birds after tying the ureters. This author considered the connective tissue the source of uric acid on account of the fact that the uric acid appears in the nucleus of the connective tissue cells before it appears at any place but the kidneys. From the nucleus the concretions spread to the body of the cell, then to the cell processes, and finally into the lymphatic system.

Meissner,[2] and later Pawlinoff,[3] found that the blood analyses of Strahl and Lieberkühn and Zalesky were faulty, and that by working with sufficient quantities uric acid can be found normally in the blood and organs of snakes and birds. Further, Pawlinoff found that after nephrotomy is properly performed on birds, uric acid concretions appear in the various organs and tissues just as they do after tying the ureters. v. Schröder[4] showed that uric acid is present in the blood of nephrotomized birds and snakes, and that after kidney extirpation uric acid concretions are found in the various organs and tissues of the snake just as they are after tying the ureters. Colasanti[5] found that the concretions formed in the various organs after tying the ureters of hens are urates, those in the ureters, uric acid. The kidneys, therefore, are not the source of uric acid in snakes or in birds.

Meissner found uric acid in especially large quantities in the liver of normal birds, although Stokvis[6] had previously missed

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[1] N. Chrzonszczewsky. Ueber den Ursprung der Lymphgefässe. Virchow's Archiv, 35, 174 (1866).

[2] G. Meissner. Beiträge zur Kenntniss des Stoffwechsels im thierischen Organismus. Zeitschr. für rationelle Med., III Reihe, 31, 144 (1868).

[3] B. Pawlinoff. Die Bildungsstätte der Harnsäure im Organismus. Virchow's Archiv, 62, 57 (1875).

[4] W. v. Schröder. Ueber die Bildungsstätte der Harnsäure im Organismus. Arch. f. Anat. u. Physiol., 1880. Suppl. Bd., p. 113.

[5] G. Colasanti. Ricerche sperimentali sulla formazione dell' acido urico. Giornale di medic. militar, 25, 1 (1881).

Also, Experimental Untersuchungen über die Bildung der Harnsäure. Moleschott's Unters., 13, 75 (1881).

[6] Stokvis. Archiv. für die höllandische Beiträge zur Natur und Heilkunde. II Serie, Bd. 2, 260 (1860).

it in the liver of the dove. Meissner, therefore, believed the liver the source of uric acid. Pawlinoff thought that the concretions are more nearly related to the blood, and that they are formed at those places where there is the least resistance to their separation from the blood. The work of Minkowski and others, which shows the liver to be the organ concerned with the formation of uric acid in birds, will be considered in the next section.

Uric Acid Formed by Synthesis in Birds

Perhaps the most important work on the uric acid is that of Minkowski.[1] He found that of the total nitrogen found in the urine of normal geese, 60 to 70 per cent is in the form of uric acid, 9 to 18 per cent in the form of ammonia, and 3 to 4 per cent in the form of urea. In the urine of geese whose livers have been extirpated, 50 to 60 per cent of the nitrogen is in the form of ammonia and very little in the form of uric acid. The amount of urea in the urine is not changed by liver extirpation.

Ammonium compounds or amido acids administered to geese with liver extirpated appeared in the urine as ammonia. Urea passed through the organism unchanged. This indicated the liver as the organ in which uric acid is synthesized.

Minkowski noted that a synthesis of uric acid from ammonia and carbon dioxide, which at that time physiologists considered probable in birds, cannot take place unless a considerable reduction takes place at the same time, and since oxidation and not reduction processes characterize the animal organism, he thought it much more likely that the ammonia combined with some other compound containing a relatively larger amount of carbon and smaller amount of oxygen than carbon dioxide. In the urine of geese with extirpated liver he found lactic acid a body answering this description. It may be mentioned that Berlinblau[2] has found lactic acid a constant constituent of normal blood.

Milroy[3] has observed that galvanic stimulation of the bird's liver aids the synthesis of uric acid.

In normal geese urine we do not find lactic acid, but in the urine

[1] O. Minkowski. Ueber den Einfluss der Leberextirpation auf dem Stoffwechsel. Arch. für exp. Path. u. Pharm., 21, 40 (1886).

[2] Berlinblau. Ueber das Vorkommen der Milchsäure im Blute und ihre Entstehung im Organismus. Arch. für exp. Path. u. Pharm., 23, p. 333 (1887).

[3] T. Milroy. The Formation of Uric Acids in Birds. Journ. of Physiol., 30, 47 (1903).

of geese with extirpated liver more than half the non-volatile portion consists of lactic acid. The ammonia and lactic acid are probably combined to form ammonia lactate, for the quantities are about in the ratio to form the salt. The highest amount of lactic acid was found after a meat diet and in starvation, and the lowest amount on a carbohydrate diet. The lactic acid, therefore, probably comes from proteid.

In brief, then, the end product of proteid metabolism in normal geese is chiefly uric acid, while in geese with extirpated liver it is chiefly ammonium lactate. From these experiments, Minkowski concluded that uric acid is synthesized in the liver in geese from ammonia and sarco-lactic acid. Horbaczewski[1] agrees with him and thinks that the artificial synthesis of uric acid from urea and the amide of trichlorlactic acid[2] strengthens this assumption. About the same time, v. Schröder[3] found that there is very little uric acid in the blood of birds, but much larger quantities, six to fourteen times as much, in the liver. This alone, however, does not indicate that uric acid is formed in the liver.

Hoppe-Seyler[4] suggested that the appearance of lactic acid in birds' urine after liver extirpation might be due to deficient oxidation on account of disturbance of the respiratory system, since Araki[5] and Zillessen[6] have found it in the urine of birds which suffered from lack of oxygen.

In a later article,[7] Minkowski answered the objection of Hoppe-Seyler by showing that extirpation of the liver is not necessary to produce ammonium lactate acid in the urine. This is brought about by simply tying the blood vessels entering the liver. If, however, but a single branch of an entering blood vessel be left open the uric acid synthesis can take place. Minkowski thus

[1] Horbaczewski. Weitere synthetische Versuche über die Konstitution der Harnsäure und Bemerkungen über die Entstehung derselben in Thierkörper. Monatshefte für Chem., 8, 584 (1887).

[2] J. Horbaczewski. Ueber eine neue Synthese und die Constitution der Harnsäure. Monatshefte für Chem., 201 (1887).

[3] v. Schröder. Ueber den Harnsäuregehalt des Blutes und der Leber der Vögel. Beiträge zu Physiol. Festschr. f. C. Ludwig, p. 89. Leipzig, 1887.

[4] Hoppe-Seyler. Beiträge zür Kenntniss des Stoffwechsels bei Säuerstoffmangel. Festschr. zu R. Virchow's 70 Geburtstage.

[5] T. Araki. Ueber die Bildung von Milchsäure und Glycose im Organismus bei Säuerstoffmangel. Zeitschr. für physiol. Chem., 5, 546 (1891).

[6] Zillessen. Ueber die Bildung von Milchsäure und Glykose in den Organen bei gestörter Circulation und bei der Blausäurevergiftung. Zeitschr. für physiol. Chem., 5, 387 (1891).

[7] Minkowski. Ueber die Ursachen der Milchsäureausscheidung nach der Leberextirpation. Arch. für exp. Path. u. Pharmak., 31, 214 (1893).

showed that the disturbance of function was due solely to the absence of the liver.

A second objection to Minkowski's conclusions was raised by Bunge,[1] who suggested that the primary disturbance in liver extirpation was the excretion of lactic acid, and that the excretion of nitrogen in the form of ammonia was caused, as in acid intoxication, by a demand for alkali to neutralize the acid. The lack of uric acid formation would then be but a secondary disturbance.

Lang[2] and Kowalewski and Salaskin[3] showed that administration of sodium bicarbonate, which was given in order to supply a base for neutralization of the acid, lowered somewhat the ammonia in the urine of birds with extirpated liver, but did not increase the amount of uric acid, and Milroy[4] has shown that the administration of a mineral acid in doses smaller than those which result in acid poisoning diminishes the transformation of ammonium salts into uric acid. This showed that a part of the ammonia is taken to neutralize the acid, but apparently this ammonia nitrogen is not taken at the expense of the uric acid nitrogen. Minkowski[5] found in fact that the ammonia of normal birds' urine, which is usually acid, was partly used to neutralize the acid present, for by administration of alkali we could decrease the amount present. Lang[2] also repeated and confirmed the experiments of Minkowski on geese with extirpated livers.

Stadthagen[6] stated that perhaps only certain antecedents of uric acid are formed in the liver from ammonia, and that perhaps some other organ, as, for example, the kidney, forms the uric acid. This idea was shown to be wrong by Kowalewski and Salaskin[3] who furnished the final proof that uric acid can be synthesized in the liver from ammonium lactate, and showed that if

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[1] G. Bunge. Lehrbuch der physiologischen und pathologischen Chemie. 4th Aufl., 338. Leipzig (1898).

[2] S. Lang. Ueber die Stickstoffausscheidung nach Leberextirpation. Zeitschr. physiol., Chem., 32, 320 (1901).

[3] K. Kowalewski und S. Salaskin. Ueber die Bildung von Harnsäure in der Leber der Vögel. Zeitschr. für physiol. Chem., 33, 210 (1901).

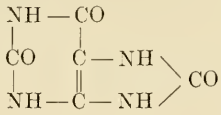
[4] T. Milroy. The Formation of Uric Acid in Birds. Jour. of Physiol. Chem., 30, 47 (1903).

[5] O. Minkowski. Ueber den Einfluss der Leberextirpation auf dem Stoffwechsel. Arch. für exp. Path. u. Pharmak., 21, 89 (1886).

[6] M. Stadthagen. Ueber das Vorkommen von Harnsäure in verschiedenen thierischen Organen, ihr Verhalten bei Leukämie und die Frage ihrer Enstehung aus den Stickstoffbasen. Virchow's Archiv, 109, 390 (1887).

blood containing ammonium lactate be passed through an isolated goose liver the ammonium lactate is changed to uric acid.

Since uric acid



is a diureïde, that is, a derivative of two molecules of urea and a non-nitrogenous body, it seems possible that ammonia may be changed first to urea and then by combination with a non-nitrogenous body to uric acid. At any rate it is known that from urea and certain acids we can synthesize uric acid in birds.

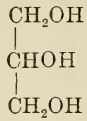
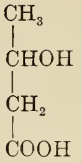
Wiener[1] showed that although when urea is fed to birds it is excreted as uric acid, yet when it is injected in large quantities directly into the arteries most of it is excreted unchanged. He believes that the explanation is that the large quantity of urea suddenly put into the system is excreted before it can obtain sufficient of the non-nitrogenous compound necessary to unite with it to form uric acid. He found that if glycerin or the aliphatic oxy-, keton-, or dibasic acids with three carbon atoms or those acids with more than three carbon atoms that easily change to such by decomposition in the body were injected together with the urea then uric acid is formed. He found

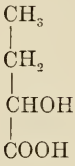
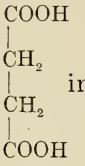
malonic acid, $CH_2(COOH)_2$ — tartronic aid, $CHOH(COOH)_2$

mesoxalic acid, $CO(COOH)_2$ — hydracrylic acid, $CH_2OH \cdot CH_2 \cdot COOH$

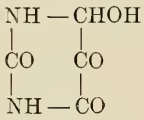
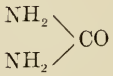
acetyl formic acid, $CH_3 \cdot CO \cdot COOH$ — lactic acid, $CH_3 \cdot CHOH \cdot COOH$

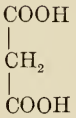
[1] H. Wiener. Ueber synthetische Bildung der Harnsäure im Tierkörper. Beiträge z. chem. Physiol. u. Path., 2, 242 (1902).

and glycerin,  most active, β-oxy-butyric acid  less active,

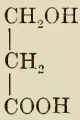
and α-oxy-butyric acid,  and succinic acid  inactive.

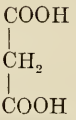
Calling to mind the synthesis of uric acid from

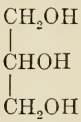
isodialuric acid,  and urea, 

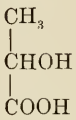
and also from malonic acid,  and urea,

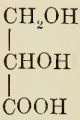
we may get a hint as to how the synthesis may take place in the living organism.

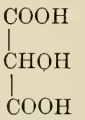

hydracrylic acid

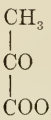

malonic acid

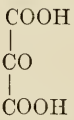

glycerin


lactic acid


glyceric acid


tartronic acid

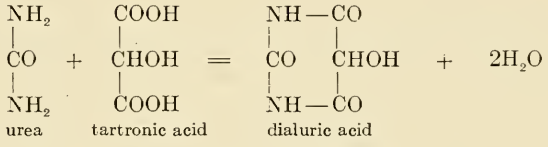

acetyl formic acid

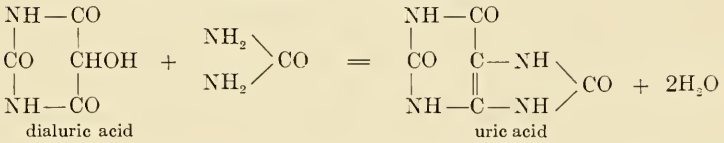

mesoxalic acid

The table shows the substances found by Wiener most active, and shows their relations to one another. The dibasic acids

containing a chain of three carbon atoms were found to be the most active. That is to say, from malonic acid, tartronic acid, and mesoxalic acid there is obtained in the urine the amount of uric acid theoretically required by a combination of one molecule of the acid with two of urea. The other active substances give a quantity less than that theoretically expected, showing that they do not wholly change to uric acid.

While a number of compounds can unite with urea to give uric acid in the normal organism, yet in the isolated liver only tartronic acid and its ureide, dialuric acid, are found active. From this we must conclude that the other active substances change first to tartronic acid, malonic and mesoxalic acid completely, the other active substances less completely. This, too, seems probable from the chemical constitution of these compounds. This synthesis of uric acid from urea and tartronic acid is represented by the following reactions, and can be carried on outside the living body:





The fact that Kowalewski and Salaskin[1] synthesized uric acid from ammonium lactate by passing the latter together with geese blood through extirpated geese livers, taken together with the fact that ammonia and lactic acid are found in geese urine after liver extirpation, indicates that the oxidation of lactic acid to tartronic acid is also a function of the liver. The dead liver, however, at least of mammals, as Wiener's work showed, is not able to carry on this process. We see, too, that the change from ammonia to urea in the synthetic formation of uric acid must take place in the liver, since it does not take place in geese with extirpated livers, and since the synthesis of uric acid from ammonia does take place in the isolated liver.

[1] K. Kowalewski und S. Salaskin. Ueber die Bildung von Harnsäure in der Leber der Vögel. Zeitschr. für physiol. Chem., 33, 210 (1901).

It may be of interest to state at this point that as late as 1893 Garrod stated [1] that uric acid is probably synthesized in the kidneys of birds from glycocoll and urea. He stated that he did not find uric acid in the blood, and that uric acid can be synthesized from glycocoll and urea "extra corpus," as proof of this theory.

It is not known whether ammonia with tartronic acid can be synthesized to uric acid by the action of fresh chopped up bird or mammal livers, that is, if the first part of the synthesis, the change from ammonia to urea, can take place in this way. The question also comes up if uric acid can be synthesized by passing through extirpated geese livers blood containing ammonia or urea together with malonic acid, hydracrylic acid, or the other bodies found to act as sources of the non-nitrogenous part of uric acid. Further, it would be of interest to know if these active bodies pass unchanged through the organism of geese with extirpated liver or to what they decompose, and to know if cut-up bird livers can bring about the change from lactic to tartronic acid in the synthesis of uric acid. We hope to make an experimental study of these questions and others suggested by these.

Wiener [2] found that carbohydrates and fats, or, more exactly, grape sugar and olive oil, as well as proteid, could serve as sources of uric acid in birds. In the case of fats, this may be accounted for by the fact that the glycerin is a source for the non-nitrogenous part of the uric acid. The action of the carbohydrates is undoubtedly due to a similar cause, as the structural formulæ of the sugars would indicate.

Uric Acid Formed in Birds by Oxidation

Mach [3] called attention to the fact that even after liver extirpation there is a small amount of uric acid still excreted by birds. He thought that this might be formed by oxidation of purin bodies from nucleo-proteids, for he found that administration of hypoxanthin increases the excretion of uric acid in birds as in

[1] A. Garrod. On the Presence of Uric Acid in the Blood of Birds, and Its Bearing upon the Formation of Uric Acid in the Animal Body. Proc. Roy. Soc., 53, 178 (1893).

[2] Wiener. Ueber synthetische Bildung der Harnsäure im Tierkörper. Beiträge z. chem. Physiol. u. Path., 2, 42 (1902).

[3] W. v. Mach. Ueber die Umwandlung von Hypoxanthin in Harnsäure im Organismus der Vögel. Arch. f. exp. Path. u. Pharmak., 23, 148 (1887).

mammals. In a later article,[1] Mach showed that the administration of hypoxanthin increases the excretion of uric acid even in hens with extirpated liver, so that this uric acid is due to an oxidation process and not, as the bulk of the uric acid excreted by birds, to a synthesis. According to more recent experiments of Milroy,[2] the administration of nucleic acid, or hypoxanthin, to birds with extirpated liver, increases the mono- and di-amino nitrogen of the urine, but not the uric acid.

The general question of a formation of uric acid by oxidation of purin bodies will be discussed at length in a later section.

Wiener [3] maintains, in common with most physiologists, that more uric acid is formed in mammals than is excreted, and that a part is decomposed and excreted as urea; and we know that in birds a large part of the urea formed is changed to uric acid. Hence, Kowalewski and Salaskin [4] have expressed the view that in both birds and mammals all the uric acid and urea formed is not excreted as such, but that some of each changes to the other.

We have seen, then, that in birds the end product of nitrogenous metabolism is chiefly uric acid, that the larger part of this is formed by synthesis, and that a small part comes from purin bodies by oxidation. The synthetic uric acid is made up of two parts, the nitrogenous and the non-nitrogenous. The nitrogenous portion comes from the proteid of the food and of the body. The non-nitrogenous part may come from the proteid, fat and carbohydrates of the body or of the food. The source of the uric acid formed by oxidation will be discussed in the section on uric acid in mammals.

Uric Acid in Mammals

Formation of Uric Acid in the Body

The question of the source of the uric acid excreted by mammals is one that has given rise to as much discussion probably as any question in the field of physiological chemistry. The early physiologists looked upon uric acid as an antecedent of urea

[1] W. v. Mach. Ueber die Bildung der Harnsäure aus Hypoxanthin. Arch. für exp. Path. u. Pharmak., 24, 389 (1888).

[2] T. Milroy. The Formation of Uric Acid in Birds. Jour. of Physiol., 30, 47 (1903).

[3] H. Wiener. Ueber Zersetzung und Bildung der Harnsäure im Tierkörper Verhandl. des 17t Kongr. für innere Medizin, 622 (1899), and Arch. für exp. Path. u. Pharmak., 42, 375 (1899).

[4] K. Kowalewsky und S. Salaskin. Ueber den Ammoniak und Milchsäuregehalt im Blute und über die Stickstoffvertheilung im Harne von Gänsen unter verschiedenen Verhältnissen. Zeitschr. für physiol. Chem., 35, 552 (1902).

in that series of proteid oxidation products, the final product of which is urea. An excretion of a large amount of uric acid they looked upon as an evidence of deficient oxidation.

It will be shown that this view of uric acid as a product of partial oxidation of proteid is an erroneous one. Since, however, some recent writers maintain that proteid can serve as a source for uric acid, not, however, in the manner in which it was believed to do so by the old writers, but after first forming urea as in birds, the question of a formation of uric acid from urea will be reserved for a later section.

We shall first discuss what are probably the most important sources of uric acid in the mammal, that is, the purin bodies and the nucleins and nucleoproteids which on decomposition give purin bodies.

FROM NUCLEO-PROTEIDS, NUCLEINS, AND PURIN BODIES

On account of the great importance of the nucleoproteids as a source of uric acid in mammals, a short sketch will be given of their chemistry and their relation to the other proteids.

Chemistry and Occurrence of the Nucleoproteids and Purins

Cohnheim [1] gives the following division of the protein bodies:

1. Simple Proteids.
   - (1.) *Albumins.*
     Seralbumin, ovalbumin, lactalbumin.
   - (2.) *Globulins.*
     Serum globulin, egg globulin, lactoglobulin, cellglobulin, plant globulins.
   - (3.) *Coagulating Proteids.*
     Fibrinogen, myosin, myogen, gluten.
   - (4.) *Nucleo-albumins.*
     Casein, vitellin, phytovitellin, nucleo-albumin of the cell protoplasm, mucilaginous nucleo-albumins.
   - (5.) *Histon.*
   - (6.) *Protamin.*
2. Derived Albumins.
   - (1.) *Acid Albumin and Alkali Albumin.*
   - (2.) *Albumoses and Peptones.*
3. Proteids.
   - (1.) *Nucleoproteids.*

[1] O. Cohnheim. Chemie der Eiweisskörper, pp. 82 und 83. Braunschweig, 1900.

Compounds of nucleic acid with (*a*) histon, (*b*) protamin, (*c*) other proteids.

(2.) *Hæmoglobin.*
Compounds of hæmatin with histon.

(3.) *Glycoproteids.*
Compounds of proteid with glucosamin and other carbohydrates.
Mucins, mucoids, helicoproteid.

4. Albuminoids.
(1.) *Collagen.*
(2.) *Keratin.*
(3.) *Elastin.*
(4.) *Spongin, fibroin, etc.*
(5.) *Amyloid.*
(6.) *Albumoid.*
(7.) *Coloring substances from proteid.*

This table shows the relation of the nucleoproteids to the other protein bodies. The proteïds are compounds of simple proteids with non-proteid bodies. They are thus in a way analogous to glucosides, which are compounds of glucose with other bodies.

The nucleoproteids were discovered by Miescher [1] and Plocz,[2] but their physical and chemical properties have only very recently been understood. On digestion with pepsin hydrochloric acid, or on boiling with hydrochloric acid, the nucleoproteids split into a simple proteid, usually either histon [3] or protamin [4] and a body containing a larger percentage of phosphorus, — a nuclein. The nuclein, too, is a compound proteid, and on further treatment with acid decomposes into a simple proteid and nu-

[1] F. Miescher. Chemische Zusammensetzung der Eiterzelle. Hoppe-Seyler's Med.-Chem. Untersuch., p. 44 (1871).

[2] P. Plocz. Kerne der Vogel- und Schlangenblutkörperschen. Hoppe-Seyler's Med.-Chem. Untersuch., p. 461 (1871).

[3] J. Bang. Studien über Histon. Zeitschr. für physiol. Chem., 27, 463 (1899).

[4] F. Miescher. Verhandl. der naturforsch. Ges zu Basel, 6, 138 (1874).

Ibid. Lachsmilch. Schmiedeberg's Arch. für exp. Path. u. Phar., 37, 100 (1896).

A. Kossel. Ueber die basischen Stoffe des Zellkerns. Zeitschr. für physiol. Chem., 22, 176 (1896).

Ibid. Ueber die Konstitution der einfachsten Eiweisstoffe. Zeitschr. für physiol. Chem., 25, 165 (1898).

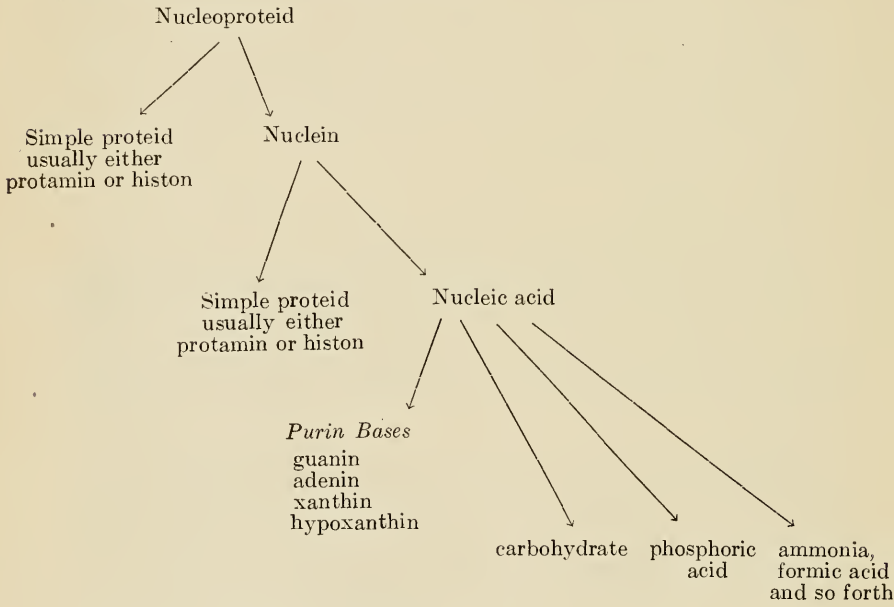
A. Mathews. Zur Chemie der Spermatozoen. Zeitschr. für physiol. Chem., 23, 399 (1897).

D. Kurajeff. Ueber das Protamin aus dem Spermatozoen der Makrele. Zeitschr. für physiol. Chem., 26, 524 (1898).

N. Morkowin. Ein Beitrag zur Kenntniss der Protamine. Zeitschr. für physiol. Chem., 28, 313 (1899).

cleic acid,[1] — a body containing still more phosphorus than the nuclein. On boiling nucleic acid for a short time with acid, certain purin bases split off,[2] also a carbohydrate,[3] usually a pentose, sometimes also a hexose, phosphoric acid, ammonia,[4] formic acid,[4] and probably other bodies.

The following sketch shows graphically how the nucleoproteids decompose on treatment with acid.



[1] R. Altmann. Ueber Nucleïnsäure. Arch. f. Anat. u. Physiol. Physiol. Abth. 1889, p. 524.

A. Kossel. Ueber die Nucleïnsäure. Arch. f. Anat. u. Physiol., 1893, p. 157, and numerous papers by Kossel and his pupils and Schmiederberg, especially in the Zeitschr. für physiol. Chem. and the Arch. f. exp. Path. u. Pharmak.

[2] Kossel und Neumann. Ueber das Thymin, ein Spaltungsprodukt der Nucleïnsäure. Ber. d. Dtsch. chem. Gesell., 26, 2753 (1893).

Kossel und Steudel. Ueber Nucleïnsäure und Thyminsäure. Zeitschr. für physiol. Chem., 22, 74 (1896).

[3] A. Kossel. Ueber die Chemische Zusammensetzung der Zelle. Arch. f. Anat. u. Physiol., 1891, 181.

Ibid. Ueber die Nucleïnsäure. Arch. f. Anat. u. Physiol., 1893, 157.

O. Hammarsten. Zur Kenntniss der Nucleoproteïde. Zeitschr. für physiol. Chem., 19, 19 (1893).

[4] Kossel und Neumann. Darstellung und Spaltungsprodukte der Nucleïnsäure. Ber. der Dtsch. chem. Gesell., 27, 2215 (1894).

Bang und Neumann. Zur Kenntniss der Nucleïnsubstanzen. Arch. f. Anat. u. Physiol., 1898, 374.

It must be understood that this sketch of the chemistry of the nucleoproteids is not intended to be thorough. It is given simply in order to show how the purin bases are obtained as decomposition products of the nucleoproteids by hydrolytic splitting "extra corpus," and therefore how they might be expected possibly to be obtained as decomposition products in the living organism. According to Kossel,[1] nucleic acid can be split into purin bases and another definite compound, thymic acid, free from the purin bases. The chemistry of the nucleoproteids is at present engaging the attention of numerous workers, for there is much to learn about the subject.

In the organism, nucleoproteid alone, not nuclein or nucleic acid, is found. Nucleoproteid is the only protein substance giving purin bodies as decomposition products. The purin bodies thus found are adenin, guanin, xanthin, and hypoxanthin. In some nucleoproteids all four bases are found, and in some others only one or two of them. The fractional amounts of proteid, purin bases, carbohydrates, and so forth in the nucleoproteids have not been accurately studied.

The nucleoproteids occur only as components of the cells of the organism, and not in solution in the animal juices, although they are sometimes found in blood serum and other fluids after cell destruction. They are the chief constituents of the cell nuclei, and therefore found in large amounts in organs rich in cells, and are probably not abundant in the cell protoplasm outside of the nucleus. Lilienfeld[2] has found the dry substance of the thymus leucocytes to consist of 77 per cent nucleoproteid (nucleo-histon), and Miescher and Schmiedeberg[3] have found the heads of the ripe spermatozoa of fish to consist of 96 per cent of nucleoproteids.

The work of Burian on the mode of combination of the purin bases in nucleic acid is of interest. It will be remembered[4] that this author showed that the purin bodies in which the hydrogen atom at position (7) is not substituted can be diazotized. He

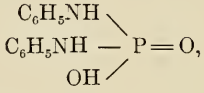
[1] A. Kossel und H. Steudel. Ueber Nucleinsäure und Thyminsäure. Zeitschr. für physiol. Chem., 22, 74 (1896).

[2] L. Lilienfeld. Zur Chemie der Leucocyten. Zeitschr. für physiol. Chem., 18, 473 (1894).

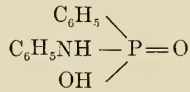
[3] F. Miescher und Schmiedeberg. Physiologische-chemische Untersuchungen ueber die Lachsmilch. Schmiedeberg's Archiv., für exp. Path. u. Pharmak. 37, 100 (1896).

[4] See page 8; also R. Burian. Diazoverbindungen der Imidazole und der Purinsubstanzen. Ber. der Dtsch. chem. Gesell., 37, 696 (1904).

then studied the nucleic acids, and found that in spite of their high content of purin base, they cannot be diazotized.[1] This is not due to something which prevents the reaction, for guanin will react with diazo-bodies in the presence of nucleic acid. Burian concludes, therefore, that either the base is not quite ready formed in the nucleic acid, or that it is combined with the rest of the nucleic acid molecule at position (7). On account of the ease with which the bases are split from the acid, he thinks that the latter condition is probably true. According to this author, the base is probably combined directly with the P rather than with O, or C, for, like certain phosphoric acid amides, for example, dianilidophosphoric acid,



and anilidophenylphosphinic acid,



they easily decompose with boiling water or HCl, but are only slowly dissolved by boiling NaOH. According to Steudel,[2] Burian's conclusions were not warranted by his results, but Burian [3] has answered Steudel's objections very satisfactorily.

Considerable work has been done recently on the occurrence of the individual purin bodies in the nucleoproteids of the different organs. According to Kossel,[4] thymus nucleic acid contains chiefly adenin. Steudel [5] found guanin, adenin, xanthin, and hypoxanthin. Jones [6] found xanthin and a small quantity of hypo-

[1] R. Burian. Zur Kenntnis der Bindung der Purinbasen im Nukleïnsäuremolekule. Ber. d. Dtsch. chem Gesell., 37, 708 (1904).

[2] H. Steudel. Zur Kenntniss der Thymusnucleïnsäuren. Zeitschr. für physiol. Chem., 42, 165 (1904).

[3] R. Burian. Zur Frage der Bindung der Purinbasen im Nukleïnsäuremolekule. Zeitschr. für physiol. Chem., 42, 297 (1904).

[4] A. Kossel. Ueber einiger Bestandtheile thierischen Zellen. Arch. für Anat. u. Physiol. (1894), 551.

[5] H. Steudel. Zur Kenntniss der Thymusnukleinsäuren. Zeitschr. für physiol. Chem., 42, 165 (1904), und 43, 402 (1905).

[6] W. Jones. Ueber die Selbstverdauung von Nukleoproteïd. Zeitschr. für physiol. Chem., 42, 35 (1904).

xanthin in thymus which had undergone autolysis. Neumann,[1] Bang,[2] Huiskamp,[3] and Kostytschew[4] have found more than one nucleoproteid in thymus glands. Bang[5] found guanin, and Bang and Raaschou[6] guanin only in the pancreas, but Levene[7] has found both guanin and adenin in fresh spleen. In spleen which has undergone self-digestion, Levene found hypoxanthin, xanthin, and some guanin, but no adenin. Schenk[8] could find only guanin and hypoxanthin in spleen which has undergone autolysis. Spleen nuclein contains guanin according to Jones,[9] adenin and guanin according to Levene.[10] In spleen which had undergone self-digestion Levene[11] found chiefly hypoxanthin. In fresh liver the nucleoproteid contains adenin, guanin, hypoxanthin, according to Levene,[11] and xanthin also according to Wohlegemuth.[12] Levene[11] found adenin, hypoxanthin, and xanthin in liver which had undergone autolytic digestion. Biondi[13] did not find any purin bases in calves' liver which had undergone self-digestion. Kossel[14] found xanthin, hypoxanthin, adenin,

[1] A. Neumann. Arch. f. Anat. u. Physiol., 344 (1898), und Verfahren zur Darstellung der Nucleïnsäuren *a* und *b* und der Nucleothyminsäure. Arch. f. Anat. u. Physiol., 552 (1899).

[2] I. Bang. Bemerkungen über das Nucleohiston. Zeitschr. für physiol. Chem., 30, 509 (1900).

Chemische Untersuchungen der lymphatischen Organe. Hofmeister's Beiträge, 4, 115 (1903).

[3] W. Huiskamp. Ueber die Eiweisskörper der Thymusdrüse. Zeitschr. für physiol. Chem., 32, 145 (1901).

Beiträge zur Kenntnis der Thymusnukleohiston. Zeitschr. für physiol. Chem., 39, 55 (1903).

[4] S. Kostytschew. Ueber Thymonukleïnsäure. Zeitschr. für physiol. Chem., 39, 545 (1903).

[5] I. Bang. Die Guanylsäure der Pancreasdrüse und deren Spaltungsprodukte. Zeitschr. für physiol. Chem., 26, 133 (1898).

[6] I. Bang und C. Raaschou. Darstellung der Guanylsäure Hofmeister's Beiträge, 4, 175 (1903).

[7] P. Levene. Darstellung und Analyse einiger Nucleïnsäure. Zeitschr. für physiol. Chem., 37, 402 (1903).

The Autolysis of Animal Organs. II. Hydrolysis of Fresh and Self-digested Glands. Am. Journ. of Physiol., 12, 276 (1904).

[8] M. Schenk. Die bei der Selbstverdauung des Pankreas auftretende Nukleïnbasen. Zeitschr. für physiol. Chem., 43, 406 (1905).

[9] W. Jones. Ueber die Selbstverdauung von Nukleoproteid. Zeitschr. für physiol. Chem., 42, 35 (1904).

[10] P. Levene. Darstellung und Analyse einiger Nucleïnsäure. Zeitschr. für physiol. Chem., 32, 541 (1901).

[11] *Ibid.* The Autolysis of Animal Organs. II. Hydrolysis of Fresh and Self-digested Glands. Am. Journ. of Physiol., 12, 816 (1904).

[12] J. Wohlegemuth. Ueber das Nukleoproteid der Leber. Zeitschr. für physiol. Chem., 42, 519 (1904).

[13] C. Biondi. Beiträge zur Lehre der fermentativen Prozesse in den Organen. Virchow's Archiv, 144, 373, 1896.

[14] A. Kossel. Ueber Nukleinsäure. Arch. f. Anat. u. Physiol. (1893), 157.

and guanin in yeast nucleic acid. Kutscher [1] found guanin and adenin in yeast which had undergone autolysis, and Schittenhelm and Schröter [2] found that xanthin and hypoxanthin are formed when the yeast nucleic acid is decomposed by bacteria. Leucocytes contain adenin and hypoxanthin.[3] In fresh spermatozoa are found adenin and guanin;[3] in self-digested spermatozoa, hypoxanthin and xanthin.[4] The red blood corpuscles contain only adenin.[5] In the fresh suprarenal gland there is guanin and adenin;[6] in that which has undergone self-digestion there is found xanthin, hypoxanthin, and 1-methylxanthin.[7] In the nucleic acid of the brain Levene [3] found adenin and guanin. We shall see later in the discussion of the metabolism of the individual purin bodies that these organs contain enzymes capable of changing the amino purins to oxypurins. This explains why it is that the same purin bases are not always found in the self-digested organs as are found in the fresh organs.

Very little nucleoproteid is found in ordinary meat,[8] but it has long been known that free hypoxanthin does occur. Strecker [9] found .022 per cent hypoxanthin, Stadeler [10] .016 per cent, and Neubauer [11] .016 to .027 per cent in beef muscle, and Scherer [12]

[1] F. Kutscher. Chemische Untersuchungen über die Selbstgährung der Hefe. Zeitschr. für physiol. Chem., 32, 59 (1901).

[2] A. Schittenhelm und F. Schröter. Ueber die Spaltung der Hefennukleïnsäure durch Bakterien, IV. Mittheilung. Zeitschr. für physiol. Chem., 41, 284 (1904).

[3] O. Schmiedeberg. Ueber die Nucleïnsäure aus der Lachsmilch. Arch. f. exp. Path. u. Pharmak., 43, 57 (1899).

P. Levene. Darstellung und Analyse einiger Nucleïnsäure. Zeitschr. für physiol. Chem., 39, 479 (1903).

[4] J. Mochizuki und Y. Kotak. Ueber die Autolyse der Stierhoden. Zeitschr. für physiol. Chem., 43, 165 (1904).

[5] Y. Inoko. Einige Bemerkungen über phosphorhaltige Blutfarbstoffe. Zeitschr. für physiol. Chem., 18, 57 (1894).

L. Lilienfeld. Zur Chemie der Leucocyten. Zeitschr. für physiol. Chem., 18, 473 (1894).

[6] Whipple and Whipple. The nucleoproteid of the suprarenal gland. Am. Journ. of Physiol., 7, 423 (1902).

[7] J. Okerblom. Die Xanthinkörper der Nebennieren. Zeitschr. für physiol. Chem., 28, 60 (1899).

[8] C. Pehelharing. Ueber das Vorhandsein eines Nukleoproteids in Muskeln. Zeitschr. für physiol. Chem., 22, 245 (1896).

[9] A. Strecker. Ueber das Sarkin. Liebig's Ann. der Chem. u. Pharm., 108, 129 (1858).

[10] Stadeler. Ueber eine leichte Darstellungsweise des Xanthins und der sich ausschliessenden Stoffe aus thierischen Organen. Liebig's Ann. der Chem. u. Pharm., 116, 105 (1860).

[11] C. Neubauer. Ueber die quantitative Bestimmung des Sarkin und Xanthins in Muskelfleisch. Frezenius' Zeitschr. für analyt. Chem., 6, 33 (1867).

[12] Scherer. Ueber Hypoxanthin, Xanthin, und Guanin, im Thierkörper und den Reichthum der Pancreasdruse an Leucin. Liebig's Ann. der Chem. u. Pharm., 112, 257 (1859).

found .014 per cent in horse flesh. These authors extracted the meat with cold water and analyzed the extract. This method does not give the hypoxanthin in the inosinic acid which Haiser [1] found in muscle and which he showed contains hypoxanthin. Kossel [2] and Monari,[3] by methods whose accuracy has been questioned, found larger amounts of hypoxanthin and also some xanthin in muscle. According to Micko,[4] meat extract contains chiefly hypoxanthin with some xanthin and a trace of adenin, but no guanin. Burian and Schur,[5] by a method which is probably more accurate than the methods of their predecessors, found .045 per cent free purin bases and .015 per cent combined purin bases.

Concerning the presence of purin bases in fish, I am aware of the work only of Schmidt-Nielson [6] and Isaac,[7] who found chiefly guanin, with smaller amounts of adenin and hypoxanthin, and traces of xanthin in pickled herring brine.

Kossel [8] and Petrén [9] analyzed milk for purin bodies, but could find none. Schmidt-Mülheim [10] stated that he isolated hypoxanthin crystals from milk, but he did not say to what extent they were present. The work of Burian and Schur [11] shows only the insignificant amount of .004 to .006 grain purin bodies per liter in milk.

The nuclein of egg yolk is only a pseudonuclein, and egg contains no purin bodies, according to Kossel,[8] Petrén,[9] and Burian and Schur.[5]

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[1] F. Haiser. Zur Kenntnis der Inosinsäure. Monatshefte für Chem., 16, 190 (1895).

[2] A. Kossel. Zur Chemie des Zellkernes. Zeitschr. für physiol. Chem., 7, 7 (1882).

Ueber Guanin. Zeitschr. für physiol. Chem., 8, 404 (1884).

[3] Monari. Arch. italiennes de Biologie, 13, 1 (1890).

[4] K. Micko. Untersuchungen von Fleisch, Hefen- und anderen Extrakter auf Xanthinkörper. Zeitschr., Unters. Nahr- und Genussm., 6, 781 (1903).

[5] R. Burian und H. Schur. Ueber die Stellung der Purimkörper in menschlichen Stoffwechsel. Pflüger's Arch., 80, 241 (1900).

[6] Schmidt-Nielson. Zur Kenntniss der Autolyse des Fischfleisches. Hofmeister's Beiträge, 3, 266 (1903).

[7] S. Isaac. Die Purinbasen der Heringslake. Hofmeister's Beiträge, 5, 500 (1904).

[8] Kossel. Medicinisch-chemisch. Untersuchungen von Hoffe-Seyler, 502. Tübingen (1871).

Ibid. Weitere Beiträge zur Chemie des Zellkerns. Zeitschr. für physiol. Chem 10, 248 (1886).

[9] K. Petrén. Nachtrag zur Mitterlung über das Vorkommen der Xanthinbasen in den Fäces. Skandinav. Archiv f. Physiol., 9, 412 (1899).

[10] Schmidt-Mülheim. Ueber Stickstoffhaltiger Körper in der Kuhmilch. Pflüger's Archiv, 30, 379 (1883).

Vegetables do not, in general, contain purin bodies, but Hall[1] has found purin bodies in peas and beans, and Salomon,[2] Reinke and Rodewald,[3] Bugarsky,[4] Schultz and Bosshard,[5] Salkowski,[6] Kossel,[7] Kossel and Neumann,[8] Micko,[9] v. Lippmann,[10] Shorey,[11] and Bressler[12] have found these bodies in small quantities in certain plants, especially in very young leguminous plants.

The Physiological Relation between the Nucleoproteids, Nucleins, Nucleic Acid, and Purin Bases, and the Formation of Uric Acid in the Mammal Organism.

Historical: The Source of Uric Acid. — On account of the fact that uric acid is easily oxidized to urea, and also that if uric acid is eaten it is excreted as urea by rabbits, according to Wöhler and Frerichs,[13] uric acid was looked upon as an antecedent of urea in the destructive metabolism of proteid. Its presence in the urine of mammals was thought to be due to incomplete oxidation processes. This is the view expressed by Liebig[14] and Lehmann[15] in their textbooks two generations ago. It was the view generally held until within about twenty years. Although historically first, we shall leave the account of the development of this idea until after treating of the physiological relations

[1] I. Hall. The Purin Bodies of Foodstuffs. Manchester, Eng. (1902).

[2] G. Salomon. Verhandlungen der physiol. Gesellschaft in Berlin, 1880–81, p. 14.

[3] Reinke und Rodewald. Untersuchungen aus dem botanischen Laboratorium in Gottingen, 2, 147.

[4] A. Bugarsky. Ueber das Vorkommen von Xanthin, Guanin, und Hypoxanthin. Zeitschr. für physiol. Chem., 8, 395 (1884).

[5] E. Schultz und E. Bosshard. Zur Kenntniss des Vorkommens von Allantoin, Asparigin, Hypoxanthin, und Guanin in den Pflanzen. Zeitschr. für physiol. Chem., 9, 420 (1885).

[6] E. Salkowski. Ueber Zuckerbildung und andere Fermentationen in der Hefe. Zeitschr. für physiol. Chem., 13, 527 (1889).

[7] A. Kossel. Arch. Physiol., 157 (1893).

[8] A. Kossel und A. Neumann. Darstellung und Spaltungsprodukte der Nucleinsäure (Adenylsäure). Ber. der Dtsch. chem. Gesell., 27, 2215 (1894).

[9] Micko. Untersuchungen von Fleisch- Hefen- und anderen Extrakten auf Xanthinkörper. Zeitschr. f. Unters. von Nahr.- und Genussmitt, 257 (1904).

[10] E. von Lippmann. Ueber Stickstoffhaltigen Bestandtheile aus Rübensaften. Ber. der Dtsch. chem. Gesell., 29, 2650 (1896).

[11] E. Shorey. Xanthin Bases in Sugar Cane. Journ. Am. Chem. Soc., 21, 432 (1899).

[12] H. Bressler. Ueber die Bestimmung der Nucleinbasen im Safte von Beta vulgaris. Zeitschr. für physiol. Chem., 41, 535 (1904).

[13] F. Wöhler und F. Frerichs. Ueber die Veranderungen, welche namentlich organische Stoffe beim Uebergang in den Harn erleiden. Liebig's Ann. der Chem. u. Pharm., 65, 335 (1848).

[14] J. Liebig. Animal Chemistry, or Organic Chemistry in its Application to Physiology and Pathology. Transl. of W. Gregory. 1843 ed. by J. Webster, Cambridge.

[15] C. Lehmann. Physiologische Chemie. Vol. I, 2d ed. (1853).

between the purin bases and uric acid. This method will be simpler, and the true explanation of the facts on which the old theory was based will be clearer.

In 1853, Virchow[1] found that the excretion of uric acid is increased in leukemia. He thought that this might be due either (*a*) to a decreased power of internal respiration on account of lack of red blood corpuscles, or (*b*) to an oxidation of hypoxanthin formed by increased activity of the spleen. The first hypothesis is based entirely on the old theory of uric acid formation. It will be considered later. The second hypothesis is based on the discovery of hypoxanthin in the watery extract of the spleen,[2] and also in leukemic blood[3] by Scherer, and on the close chemical relationship shown by him[2] to exist between hypoxanthin and uric acid. In a later article[4] Scherer confirmed his earlier discovery and found in leukemic blood not only hypoxanthin, but also uric acid. Ranke,[5] likewise, who found the excretion of uric acid increased in leukemia, attributed it to the hypoxanthin produced by the activity of the spleen. He believed that normally the uric acid comes from the spleen. Meissner,[6] too, believed that the uric acid is derived normally from the xanthin bases of the tissues.

Salkowski[7] maintained that if the increased excretion of uric acid in leukemia is due to defective oxidation, other products of defective oxidation should be found in the urine. He could find, however, no products which could not be explained by assuming an increased activity of the spleen.[8] He therefore expressed the view that the increased secretion of uric acid in leukemia which had been noticed by Virchow,[1] Thierfelder and

[1] R. Virchow. Zur pathologischen Physiologie des Blutes. Virchow's Archiv, 5, 43 (1853).

[2] Scherer. Ueber einen im thierischen Organismus vorkommenden dem Xanthinoxyd verwandten Körper. Liebig's Ann. der Chem. u. Pharm., 73, 328 (1850).

[3] *Ibid.* Untersuchungen über das Blut bei Leukämie. Verhandl. der physik. mediz. Gesellsch. zu Würzburg, 2, 321 (1851).

[4] *Ibid.* Beitrag zur Geschichte der Leukämie. Chemische Untersuchungen des Blutes. Verhandl. der physik. mediz. Gesellsch. zu Würzburg, 7, 123 (1856).

[5] H. Ranke. Beobachtungen und Versuche über die Ausscheidung der Harnsäure beim Menschen. München, 1858.

[6] G. Meissner. Beiträge zur Kenntnis des Stoffwechsels im thierischen Organismus. Zeitschr. für rationelle Med., 3 Reihe, 31, 234 (1868).

[7] E. Salkowski. Beiträge zur Kenntniss der Leukämie. Virchow's Archiv, 50, 174 (1870).

[8] *Ibid.* Weitere Beiträge zur Kenntniss der Leukämie. Virchow's Archiv, 52, 58 (1871).

Uhle,[1] H. Ranke,[2] Parkes,[3] Mosler,[4] Berell,[5] Schultzer,[6] Pettenkofer and Voit,[7] Jacubasch,[8] Reichhardt,[9] and Hofmann,[10] was due to an oxidation of the hypoxanthin coming from increased activity of the spleen.

The view that the high excretion of uric acid in leukemia is due to an oxidation of hypoxanthin present in the blood through increased activity of the spleen did not seem to explain the physiological source of uric acid, although Ranke and Meissner believed that even normally uric acid is derived from hypoxanthin. It was not believed that hypoxanthin is present in the tissues of the body and in the food in large enough quantities to serve as source for all the uric acid excreted. In any case, however, the ultimate source of uric acid was still supposed to be proteid, for hypoxanthin was considered a decomposition product of proteid. Thus, Salomon [11] and Chittenden [12] obtained hypoxanthin and xanthin by the action of pancreas ferment on fibrin. Although Drechsel [13] had suggested that the small amount of xanthin bases

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[1] T. Thierfelder und J. Uhle. Ein Fall von Leukämie. Arch. f. physiol. Heilk., 15, 441 (1856).

[2] H. Ranke. Beobachtungen und Versuche über die Ausscheidung der Harnsäure beim Menschen. München, 1858. Schmidt's Jahrb., 104, 22 (1859).

[3] Parkes. The Composition of Urine. London, 331 (1860).

[4] E. Mosler und W. Körner. Zur Blut und Harnanalyse bei Leukämie. Virchow's Archiv, 25, 142 (1862). *Also,*

F. Mosler. Zur Diagnose der lienalen Leukämie und der chemischen Beschaffenheit der Transudate und Secrete. Virchow's Archiv, 37, 43 (1868).

[5] C. Berell. Zur Kasuistik der Leukämie. Schmidt's Jahrb., 142, 167 (1869) from Medical Times and Gazette, March 14, p. 284 (1868).

[6] Steinberg. Ueber Leukämie. Inaug. Dissert., Berlin, 1868.

[7] M. v. Pettenkofer und C. Voit. Ueber den Stoffverbrauch bei einem leukämischen Manne. Zeitschr. für Biol., 5, 319 (1869).

[8] H. Jacubasch. Beiträge zur Harnanalyse bei lienaler Leukämie. Virchow's Archiv, 43, 196 (1868).

[9] E. Reichhardt. Blut und Harn bei Leukämie. Jenaische Zeitschr. f. Medizin und Naturwissenschaften, 5, 389 (1870).

[10] K. Hofmann. Harnbeschaffenheit bei Leukämie lienalis. Wien Med. Wochenschrift, 20, 981 (1870), and 20, 1036 (1870).

[11] G. Salomon. Bildung von Xanthinkörper aus Eiweiss durch Pancreasverdauung. Ber. der Dtsch. chem. Gesell., 11, 574 (1878).

Ibid. Ueber die Verbreitung und Entstehung von Hypoxanthin und Milchsäure im tierischen Organismus. Zeitschr. für physiol. Chem., 2, 65 (1878).

H. Krause und G. Salomon. Weitere Mittheilungen über die Bildung von Xanthinkörpern aus Eiweiss. Ber. der Dtsch. chem. Gesell., 12, 95 (1879).

G. Salomon. Ueber die Entstehung von Hypoxanthin aus Eiweisskörpern. Ber. der Dtsch. chem. Gesell., 13, 1160 (1880).

[12] R. Chittenden. On the Formation of Hypoxanthin from Albumin. Journ. of Physiol. 2, 28 (1879–80), and Untersuchungen des physiologische Instituts der Univers. Heidelberg, Bd. 2. Heft 4.

[13] E. Drechsel. Zur Frage nach der Entstehung von Hypoxanthin aus Eiweisskörpern. Ber. der Dtsch. chem. Gesell., 13, 240 (1880).

might come from impurities such as the white blood corpuscles enclosed by the fibrin, yet even in 1882 Salkowski and Leube [1] considered hypoxanthin a decomposition product of proteid.

About 1880 Kossel [2] began to study the nucleins which had been discovered by Miescher [3] ten years before. In his first research on the subject, Kossel found hypoxanthin as a decomposition product of the nucleins. As a result of this and later researches,[4] he soon came to the conclusion that the nucleins alone are the physiological source of the purin bases. As a result of the determination of the free purin bases and those combined in nucleins in the tissues, he found that the purin bases are present in much larger quantities than had previously been supposed.[5] He suggested that the purin bases might be the physiological antecedents of uric acid and showed that the objection that these bases are not present in the tissues in large enough quantities to serve as the physiological source of uric acid could no longer hold. Salomon soon admitted that his earlier belief that the xanthin bases can be derived from albumin is erroneous.[6]

Kossel [7] later showed that the muscles of those animals, the chief end product of whose nitrogenous metabolism is uric acid, are richer in purin bodies than the muscles of mammals, and that leukemic blood is richer in hypoxanthin than normal blood. Previous to this Chrzonszczewski [8] and Pawlinoff [9] had shown that in the tissues of birds whose ureters have been tied, the uric acid concretions are abundant near the cell nuclei. Benecke [10] and Senator [11] had expressed the idea that urea and uric acid are

[1] Salkowski und Leube. Die Lehre vom Harn, pp. 98, 99, 106. Berlin (1882).

[2] A. Kossel. Ueber das Nuclein der Hefe. Zeitschr. für physiol. Chem., 3, 284 (1879).

[3] Miescher. Medic-chem. Untersuchungen von Hoppe-Seyler, 441.

[4] A. Kossel. Ueber die Herkunft des Hypoxanthins in den Organismen. Zeitschr. für physiol. Chem., 5, 152 (1881).

Ibid. Ueber das Nuclein der Hefe. Zeitschr. f. physiol. Chem., 4, 290 (1880).

Ibid. Ueber Xanthin und Hypoxanthin. Zeitschr. für physiol. Chem., 6, 422 (1882).

Ibid. Zur Chemie des Zellkernes. Zeitschr. für physiol. Chem., 7, 7 (1882–3).

[5] *Ibid.* Ueber die Verbreitung des Hypoxanthins im Thier- und Pflanzenreich. Zeitschr. für physiol. Chem., 5, 267 (1881).

[6] G. Salomon. Zur Physiologie der Xanthinkörper Vortrag gehalten in der physiol. Gesell. zu Berlin am 20 mai, 1881. Du Bois Archiv, 361 (1881).

[7] A. Kossel. Zur Chemie des Zellkernes. Zeitschr. für physiol. Chem., 7, 7 (1882).

[8] N. Chrzonszczewski. Ueber der Ursprung der Lymphgefässe. Virchow's Archiv, 35 174 (1866).

[9] C. Pawlinoff. Die Bildungsstätte der Harnsäure in Organismus. Virchow's Archiv, 62, 57 (1875).

[10] Benecke. Grundlinien der Pathologie des Stoffwechsels (1874).

[11] Senator. Ueber Podagra. Ziemssen's Handbuch der spez. Pathol. und Therapie (1875).

derived from different sources. They did not, however, state just what they believed to be the source of uric acid. Kerner,[1] the first to attempt direct feeding experiments with a purin base, fed guanin to rabbits but could not observe any increase in the excretion of uric acid.

Baginsky[2] then attempted direct feeding experiments. He fed hypoxanthin to dogs, but could observe no increase in the excretion of uric acid, although the hypoxanthin did not appear in the urine. Nencki and Sieber[3] likewise could observe no increased excretion of uric acid after feeding xanthin to dogs, but there was an increase of the excretion of urea. The xanthin did not reappear in the urine. This work was confirmed a dozen years later by Krüger and Salomon.[4]

Ebstein[5] expressed the view that the negative results obtained by feeding purin bases to animals with the expectation of obtaining an increase in the excretion of uric acid is due to the fact that some special conditions lacking in the artificial experiments determine the formation of uric acid normally from the xanthin bases of the body.

Stadthagen[6] repeated the feeding experiments and attempted to increase the uric acid excretion by feeding purin bodies. He, likewise, obtained negative results. He then took up Ebstein's hypothesis and believed it possible that although outside the body purin bases are obtained by decomposition of nucleins, yet in the body uric acid itself is obtained and not the bases. He carried out feeding experiments, giving nucleins instead of purin bases. In this case, too, he obtained no increase in the excretion of uric acid. At first he believed that possibly this nuclein artificially obtained might act in a different manner from the living nucleoproteid in the cell, but since he could show no relation between the uric acid excretion and the decomposition of cell nuclei, he returned

[1] Kerner. Ueber das Verhälten des Guanins. Annal. d. Chem. u. Pharm., 103, 249 (1857).

[2] A. Baginsky. Ueber das Vorkommen von Xanthin, Guanin, und Hypoxanthin. Zeitschr. für physiol. Chem., 8, 395 (1883).

[3] M. Nencki und N. Sieber. Ueber eine neue Methode die physiologische Oxydation zu messen und über die Einfluss der Gifte und Krankheiten auf dieselbe. Pflüger's Archiv, 31, 319 (1883).

[4] M. Krüger und G. Salomon. Die Konstitution des Heteroxanthins und seine physiologische Wirkung. Zeitschr. für physiol. Chem., 21, 168 (1885).

[5] W. Ebstein. Die Natur und Behandlung der Gicht, 98 (1882).

[6] Stadthagen. Ueber das Vorkommen der Harnsäure in verscheidenen tierischen Organen, ihr Verhalten bei der Leukämie und die Frage ihrer Entstehung aus den Stickstoffbasen. Virchow's Archiv, 109, 390 (1887).

to the old view that the uric acid is derived from proteid. Gumlich [1] later repeated these nuclein feeding experiments, and proved that the nucleins were absorbed, something Stadthagen had not done, but still found no increased excretion of uric acid. He did not, however, conclude from his results that uric acid cannot be derived from the nucleins.

Horbaczewski [2] then took up the work. He found that on digesting freshly cut-up spleen with defibrinated blood and air, uric acid is obtained. The amount of uric acid obtained varies with the quantity of spleen used and the length of time of digestion. Blood free from oxygen does not act. Therefore the formation of uric acid is probably an oxidation process in part. Horbaczewski expressed the view that the uric acid comes from the lymphatic elements of the spleen, a fact which he proved later.

In a second article, Horbaczewski [3] showed that if spleen be digested with water instead of with blood, purin bases instead of uric acid are obtained. These he could not oxidize to uric acid by digestion with arterial blood. This seemed to indicate the truth of Stadthagen's view that the uric acid and purin bodies are derived from a common antecedent, but that the purin bases once formed cannot be oxidized to uric acid in the body. If nuclein be used instead of cut-up spleen, the same results are obtained, and experiments on rabbits and man showed that administration of nuclein with the food gave a decided increase in the amount of uric acid excreted. The negative results obtained by Stadthagen and Kerner were attributed by Horbaczewski to the use of dogs. These he thinks react differently from rabbits and man in respect to uric acid excretion.

The objection of Kossel [4] and Wulff [5] that Horbaczewski did not have an accurate method of separating purin bases and uric acid and consequently, that, instead of chiefly uric acid, Horbaczewski might have obtained chiefly purin bases in many of his experi-

[1] G. Gumlich. Ueber die Aufnahme der Nucleine in den theirischen Organismus. Zeitschr. für physiol. Chem., 18, 508 (1894).

[2] Horbaczewski. Untersuchungen über die Entstehung der Harnsäure im Säugetheirorganismus. Monatshefte für Chemie, 10, 624 (1889).

[3] *Ibid.* Beiträge zur Kenntniss der Bildung der Harnsäure und der Xanthinbasen, sowie der Entstehung der Leukocytose im Säugetheirorganismus. Monatshefte für Chemie, 12, 221 (1891).

[4] H. Kossel. Ueber Nucleinsäure. Vortrag gen. in d. physiol. Gesell. zu Berlin am 14 Oktober (1892). Du Bois Archiv, 157 (1893).

[5] C. Wulff. Zum Nachweiss der Harnsäure in den Organen. Zeitschr. für physiol. Chem., 17, 634 (1893).

ments was met by Horbaczewski,[1] who declared that he always had either uric acid entirely or purin bases entirely as end products of digestion. Later [2] he confirmed his results by using a more accurate method of separation for uric acid and purin bases. The results of Horbaczewski were completely confirmed by Giacosa.[3]

Spitzer [4] repeated the work of Horbaczewski. He found that the slight bacterial decomposition which Horbaczewski found necessary to obtain his results is not necessary. Further, he contested the idea that uric acid and purin bodies come from a common antecedent, and that purin bodies once formed cannot change to uric acid. He called attention to the work of Salomon [5] and Salkowski,[6] who found purin bases in extracts of liver and spleen, and showed that this gradually disappears and changes to uric acid on digestion with blood and air. Further, he showed that if weighed amounts of xanthin or hypoxanthin are added to the mixture of blood and spleen in one of these digestion experiments, they are oxidized to uric acid, thus giving a complete proof that purin bases can act as antecedents of uric acid in the animal body. Guanin and adenin could likewise be changed to uric acid, but not in such large quantities as xanthin and hypoxanthin. He found that if the spleen or liver were left out in the experiment that blood alone could not change the bases to uric acid. There is present in those organs something necessary to carry on the oxidation. This work was further confirmed by Weintraud,[7] Mayer,[8] Bohland,[9] Richter,[10] Wiener,[11] and others, so

[1] Horbaczewski. Bemerkungen zum Vortrage des Herrn Kossel: Ueber Nucleinsäure. Du Bois Archiv, 109 (1893).

[2] *Ibid.* Ueber die Trennung der Harnsäure von den Xanthinbasen. Zeitschr. f. physiol. Chem., 18, 341 (1894).

[3] P. Giacosa. Ueber die Bildung der Harnsäure im Organismus. Maly's Jahresb. über die Fortschritte der Thierchemie, 21, 182 (1891), and Weiner Med. Blätter, 1890, No. 32.

[4] W. Spitzer. Die Ueberführung von Nucleïnbasen in Harnsäuren durch die Säuerstoffübertragende Wirkung von Gewebsauszügen. Pflüger's Archiv, 76, 192 (1899).

[5] G. Salomon. Zur Physiologie der Xanthinkörper. Vortrag geh. in d. physiol. Gesell. zu Berlin am 20 Mai, 1881. Du Bois Archiv, 361 (1881).

[6] E. Salkowski. Ueber Autodigestion der Organe. Zeitschr. für klin. Medizin, 17, Suppl., 77 (1890).

[7] W. Weintraud. Ueber die Einfluss des Nukleins der Nahrung auf die Harnsäurebildung. Berl. klin. Wochenschrift, 32, 405 (1895).

[8] P. Mayer. Ueber den Einfluss von Nucleïn und Thyreoidinfütterung auf die Harnsäureausscheidung. Deutsche Med. Wochenschrift, 22, 186 (1896).

[9] Bohland. Ueber den Einfiuss einiger Arzneimittel auf die Bildung und Ausscheidung der Harnsäure. Münchener Mediz. Wochenschrift, 46, 505 (1899).

[10] P. Richter. Ueber die Harnsäureausscheidung und Leukocytose. Zeitschr. für klin. Medizin, 27, 290 (1895).

[11] H. Wiener, Ueber Zersetzung und Bildung der Harnsäure im Tierkörper. Verhandl. des 17t Kongr. f. innere Med., 622 (1899), and Arch. für exp. Path. u. Pharmak., 42, 375 (1899).

that there is now no question that nucleoproteids, nucleins, and purin bases can serve as sources for uric acid in the animal organism. Only Kutscher and Seeman [1] have doubted in recent times that uric acid does not come from nucleins. They base their objection on the fact that they obtained urea and imido urea, but no uric acid in the oxidation of nucleic acid by calcium permanganate. This, of course, cannot be considered an objection in view of the results of direct experiments; besides, Burian [2] has shown that calcium permanganate oxidizes uric acid to urea and oxalic acid, and therefore any uric acid formed from the purins of the nucleic acid in the experiments of Kutscher and Seeman is destroyed.

Uric Acid derived from the Nucleoproteids and Purins of the Body. *Uric Acid from the Leucocytes.* — As a result of his work, Horbaczewski [3] expressed the view that just as fresh blood acts on the lymphatic elements of the spleen to form uric acid, so we might by analogy believe that in the living organism the blood acts on its own leucocytes to form uric acid. He explained the increased excretion of uric acid in leukemia by assuming that the large number of leucocytes in the blood in this disease gives rise, by the oxidizing action of the blood, to a correspondingly large amount of uric acid. He called attention to the coincidence of the digestive leucocytosis and the increased excretion of uric acid shown by Ranke [4] to take place after ingestion of large quantities of proteid food. He noted, too, that the blood of children is richer in leucocytes than that of adults, that the blood of men is richer in leucocytes than that of women, that the blood of well-nourished individuals is richer in leucocytes than the blood of poorly nourished ones, and that, correspondingly, children excrete relatively more uric acid than adults, men excrete more uric acid than women, and well-nourished individuals excrete more uric acid than poorly nourished ones.

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[1] F. Kutscher und Seeman. Die Oxydation der Thymusnukleïnsäure mit Calciumpermanganate. Ber. der Dtsch. chem. Gesell., 36, 3023 (1903). Also
Ueber die Oxydation der Hefenukleïnsäure mit Kalziumpermanganate. Zentralbl. für Physiol., 17, 715 (1904).

[2] R. Burian. Zu den Versuchen von Kutscher und Seemann über die Oxydation der Nukleïnsäuren mit Calciumpermanganate. Zeitschr. für physiol. Chem., 43, 494 (1905).

[3] J. Horbaczewski. Untersuchungen über die Entstehung der Harnsäure im Säugetheirorganismus. Monatshefte für Chemie, 10, 624 (1889).

[4] Ranke. Beobachtungen und Versuche über die Ausscheidung der Harnsäure. Habilitationsschrift, München (1858).

In a second article [1] Horbaczewski stated his belief that the formation of uric acid is an expression of the decomposition of tissues rich in nuclein. Since the tissues of the body which are rich in nucleins, with the exception of the leucocytes, do not undergo rapid metabolism, that is to say, are not quickly formed and quickly decomposed,[2] Horbaczewski assumed that the uric acid excreted by mammals comes from a decomposition of leucocytes. He reiterated what he said in his earlier article in confirmation of this view and added new arguments. In regard to the coincidence of the digestive leucocytosis and the increased excretion of uric acid after meals, he showed that neither is so marked after eating vegetable food as after eating meat, and that in certain diseases in which the digestive leucocytosis is missing, there is no increased excretion of uric acid after meals. He stated that when this digestive leucocytosis disappears, the leucocytes serve to build up the tissues of the body, or to form, perhaps, red blood corpuscles, but that in any case, the nuclein in the leucocytes decomposes and gives uric acid as one of its decomposition products.

Horbaczewski then studied the action of drugs on leucocytosis and uric acid excretion. Ranke,[3] Kerner,[4] Prior,[5] and Kumagawa [6] had found that quinine decreases the excretion of uric acid, and Binz [7] had found that it decreases the number of leucocytes in the blood. Chittenden [8] had found that antipyrin decreases the excretion of uric acid. Umbach [9] did not find antipyrin to have any effect on the excretion of uric acid, while Kumagawa,[6] on the other hand, found it to increase the excretion of uric acid.

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[1] J. Horbaczewski. Beiträge zur Kenntniss der Bildung der Harnsäure und der Xanthinbasen, sowie der Entstehung der Leucocytose im Säugethierorganismus. Monatshefte für Chemie, 12, 221 (1891).

[2] Voit. Physiol. d. allg. Stoffwechsels und d. Ernährung, 1881, p. 274.

[3] Ranke. Beobachtungen und Versuche über die Ausscheidung der Harnsäure. Habilitationsschrift, München (1858).

[4] G. Kerner. Beiträge zur Kenntniss der Chininresorption. Pflüger's Archiv, 3, 93 (1870).

[5] Prior. Ueber den Einfluss des Chinin auf den Stoffwechsel des gesunden Organismus. Pfluger's Archiv, 34, 237 (1884).

[6] M. Kumagawa. Ueber die Wirkung einiger antipyretische Mittel auf den Eiweissumsatze im Organismus. Virchow's Archiv, 113, 134 (1888).

[7] Binz. Das Chinin, etc. Berlin, 1875, p. 12.

[8] R. Chittenden. Ueber den Einfluss von Urethan, Antipyrin, und Antifibrin auf den Eiweissumsatz. Zeitschr. für Biol., 25, 496 (1889).

[9] M. Umbach. Ueber den Einfluss des Antipyrins auf die Stickstoffausscheidung. Arch. für exp. Path. u. Pharmak., 21, 161 (1886).

Antifebrin had been found by Chittenden,[1] and pilocarpin by Mares,[2] to increase the excretion of uric acid. Horbaczewski repeated this work and found that quinine and atropin decrease the excretion of uric acid and likewise the number of leucocytes in the blood, and that pilocarpin increases the excretion of uric acid and the number of leucocytes in the blood. On the other hand, antipyrin and antifebrin increase the number of leucocytes but decrease the uric acid excretion. Horbaczewski explained the action of antipyrin and antifebrin by assuming that they cause a decreased decomposition of leucocytes, thus decreasing the excretion of uric acid and increasing the quantity of leucocytes present.

For further confirmation of his theory, Horbaczewski then turned to pathological conditions. The increased excretion of uric acid in leukemia seemed to be in accord with his theory. The relation between the decomposition of tissue and the increased excretion of uric acid found by Fränkel and Rohmann[3] in phosphorous poisoning seemed plain from the standpoint of this theory. The increased excretion of uric acid in fevers noticed by Cario[4] and Baftalowsky,[5] and in inanition and cachexia is, according to Horbaczewski, an expression of the decomposition of tissue rich in nuclein. Frey and Heiligenthal found that hot air baths increase the excretion of uric acid, and Horbaczewski found that they cause, likewise, increase of the leucocytes of the blood.

Horbaczewski believed that the uric acid excreted comes almost exclusively from the leucocytes of the blood, and that the nuclein in the food need not necessarily be assumed to decompose and oxidize to uric acid, but that it may act like certain drugs to increase the number of leucocytes and thus indirectly increase the uric acid excretion. The fact that the intensity of increase in the excretion of uric acid and the increase in the number of

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[1] R. Chittenden. Ueber den Einfluss von Urethan, Antipyrin, und Antifebrin auf den Eiweissumsatz. Zeitschr. für Biol., 25, 496 (1898).

[2] F. Mares. Sur l'origine de l'acide urique chez l'homme. Archives slaves de Biologie, 3, 207 (1888).

[3] Frænkel und Rohmann. Phosphorvergiftung bei Hühnern. Zeitschr. für physiol. Chem., 4, 439 (1880).

[4] Cario. Ueber den Einfluss des Fiebers und der Inanition auf die Ausscheidung der Harnsäure und der übrigen wesentlichen Harnbestandtheile. Preisschrift Göttingen, (1888).

[5] Baftalowsky. Die Methoden der Harnsäurebestimmungen. Maly's Jahresb. über die Fortschritte der Thierchem., 18, 128 (1889).

leucocytes of the blood is not parallel, and that we may have a large quantity of leucocytes in the blood and a relatively small increase in the excretion of uric acid, and, vice versa, he explained by saying that the size of the individual leucocytes and the amount of nuclein in them is variable.

The view that the uric acid is derived from the leucocytes had been expressed by Benecke [1] many years before Horbaczewski's article appeared, but the latter seems to have brought more facts to uphold his theory or to have expressed it in a more decided manner, for he is given the credit of being the author of the theory by practically all writers.

A number of physiologists published results which seemed to confirm the views of Horbaczewski. Sticker,[2] Fränkel,[3] and Gumprecht,[4] for example, found that in leukemia there is a parallelism between the number of leucocytes in the blood and the excretion of uric acid, and Gumprecht showed that in leukemia there is also an increased decomposition of leucocytes as well as an increased formation. Dunin and St. Nowaczek[5] found that in pneumonia there is an increased excretion of uric acid with the increased leucocytosis. This had been noticed earlier by Gardes.[6] Kühnau[7] found an increased excretion of uric acid in leukemia, pneumonia at the crisis, and in other diseases in which there is an increase of leucocytes, as well as in cases where the leucocytosis is brought about artificially. This author found, too, that as the leucocytosis disappears in pneumonia, the uric acid excretion increases, a fact which he thought indicated that the uric acid is derived from these decomposed leucocytes. Pope,[8] however, believed that the increased excretion of uric acid in pneumonia comes from the leucocytes of the exudate, since the

[1] Cited by Girandeau. Note sur un cas de Leukocythèmie splénique. Arch. de physiologie norm. et pathol., No. 8, 1884. Girandeau does not give the original reference.

[2] G. Sticker, Beiträge zur Pathologie und Therapie der Leukämie. Zeitschr. für klin. Medizin, 14, 80 (1888).

[3] A. Fränkel. Ueber akute Leukämie. Deutsche med. Wochenschrift, vol. 21, pp. 639, 663, 676, 699, and 712 (1895).

[4] Gumprecht. Leukocytenzerfall im leukämischen Blute. Verhandlungen des 17 Kongr. für innere Médizin, 314 (1896).

[5] T. Dunin und St. Nowaczek. Ueber Harnsäureausscheidung bei croupöser Pneumonie. Zeitschr. für klin. Medizin, 32, 1 (1897).

[6] Gardes. Ueber Stickstoff und Harnsäureausscheidung bei verscheidenen Krankheiten (1890).

[7] W. Kühnau. Experimentelle und klinische Untersuchungen über das Verhältniss der Harnsäureausscheidung zur Leukocytose. Zeitschr. für klin. Med., 28, 534 (1895).

[8] C. Pope. Zur Kenntniss der Beziehungen zwischen Hyperleukocytose und Alloxurkörperausscheidung. Centralblatt für innere Medizin, 20, 657 (1899).

increased excretion seems to occur after the absorption of the exudate and not when the leucocytosis is present.

Daniel[1] found that quinine, which lowers the number of leucocytes, prevents also an increased excretion of uric acid after thymus feeding. Since thymus feeding alone causes an increased excretion of uric acid, Daniel explained his results by saying that thymus feeding causes a hyperleucocytosis, and that the hyperleucocytosis causes increased excretion of uric acid. When the hyperleucocytosis is prevented from occurring by the quinine, the increased excretion of uric acid does not take place. It has been shown by Ranke,[2] however, that quinine likewise causes a decreased excretion of uric acid, so that in Daniel's experiments the decreased excretion of uric acid by quinine merely neutralizes the increased excretion usually brought about by thymus feeding. As a matter of fact, Burian and Schur[3] showed this to be the case by calculation from Daniel's results.

Milroy and Malcolm[4] found that after thymus feeding the excretion of phosphorus was increased more than could be explained by the assumption that it comes from a direct decomposition and oxidation of the thymus nuclein. They looked upon this fact as a confirmation of Horbaczewski's view that the nuclein merely increases the decomposition of the leucocytes. The P_2O_5 excreted, however, is not a measure of the absorption of nuclein. Other factors come into play. Kühnau,[5] for example, observed in malaria an increased excretion of uric acid and at the same time a decreased excretion of P_2O_5. The same thing occurred in the metabolism of an animal poisoned with pyrogallol. Jacob and Bergell[6] noted that there is a retention of P_2O_5 by the body if the food is poor in phosphorus. These authors found an increased excretion of uric acid after feeding spleen to an anemic patient, but found that a large part of the phosphorus from the spleen nuclein was retained. On feeding nuclein to a gouty patient,

[1] Daniel. Inaug. Dissert., Bonn (1898).

[2] Ranke, H. Beobachtungen und Versuche über die Ausscheidung der Harnsäure bei Menschen. München (1858).

[3] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. 1. Mitteilung. Pflüger's Archiv, 80, 241 (1900).

[4] T. Milroy and J. Malcolm. The Metabolism of the Nucleins under Physiological and Pathological Conditions. Journ. of Physiol., 23, 217 (1899).

[5] W. Kühnau. Ueber das Verhalten des Stoffwechsels und der weissen Blutelemente bei Blutdissolution. Dtsch. Arch. f. klin. Med., 58, 339 (1897).

[6] P. Jacob und P. Bergell. Ueber den Einfluss nukleïnhaltiger Nährung auf Blut und Stoffwechsel unter besonderer Berücksichtigung des Phosphorsäurestoffwechsels. Zeitschr. für klin. Med., 35, 171 (1898).

Vogt[1] observed that the phosphorus from the nuclein was excreted very quickly, the uric acid only later. The phosphorus excretion depends somewhat, too, on the excretion of calcium.[2]

Williamson[3] thinks he has shown a relationship between uric acid excretion and leucolysis.

The view of Horbaczewski that an increased excretion of uric acid might take place without a coincident leucocytosis, provided that the increased uric acid came from the decomposition of leucocytes especially rich in nucleoproteid, had a possible confirmation in the work of Neusser.[4] This author found that in gout and certain other diseases there were granules around the nuclei of the leucocytes which colored with basic dyes. He interprets them as an overproduction of nuclear material. We shall see later, however, that Neusser's results have been questioned.

Bohland[5] confirmed the work of Horbaczewski, showing the influence of certain drugs on the excretion of uric acid, but gave his results a different interpretation. He believes that under the influence of pilocarpin and sodium salicylate more uric acid comes from the decomposition of the nucleoproteid than normally, while by using atropin, tannic acid, and chinin more purin bases are formed, or more uric acid is oxidized to allantoin or urea.

On the other hand, before the publication of Horbaczewski's theory, Girandeau[6] studied the leucocytosis and the excretion of uric acid in leukemia, but could find no relation between them. He found a very low number of leucocytes in a case in which the

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[1] H. Vogt. Ein Stoffwechselversuch bei akuter Gicht. Deutsche. Arch. für klin. Medizin, 71, 21 (1901).

[2] Tereg und Lehmann. Das Verhalten der Calcium Phosphate im Organismus der Fleischfresser. Pflüger's Archiv, 32, 122 (1883).

Schetelig. Ueber der Herstammung und Ausscheidung des Kalkes im Gesunden und kranken Organismus. Virchow's Archiv, 82, 437.

E. Lehmann. Zur Wirkung des kohlensäuren Kalkes und der kohlensäuren Magnesia. Berl. klin. Wochenschrift, 21 (1882), and Zur Wirkung des kohlensäuren Kalkes. Berl. klin. Wochenschrift, 31, 23 (1893).

See, also, Goldthwait, Painter, and Osgood. The preliminary report of a series of Metabolism Observations made in Atrophic Arthritis, Hypertrophic Arthritis, Osteitis Deformans and the Normal. American Medicine, 7, 547, and 590 (1904).

[3] O. Williamson. On the Relation Existing between Uric Acid Excretion and the Breaking Down of the White Blood Corpuscles. Lancet, 1903, I, 1580.

[4] Neusser. Ueber einen besonderen Blutbefund bei uratische Diathese. Wiener klin. Wochenschrift, 7, 727 (1894).

[5] Bohland. Ueber den Einfluss einiger Arzneimittel auf die Bildung und Ausscheidung der Harnsäure. Münchener Mediz. Wochenschrift, 46, 505 (1899).

[6] Girandeau. Note sur un cas de Leukocythèmie splénique. Arch. de physiologie norm. et pathol., No. 8, 1884.

uric acid had increased to four times the normal amount. After Horbaczewski's work, Matthes[1] found the amount of uric acid excreted in leukemia normal, and Jacob and Krüger[2] likewise found no parallelism between the uric acid excretion and the leucocytosis in leukemia, although the uric acid excretion was somewhat high. Richter[3] studied the leucocytosis and the excretion of uric acid, not only in leukemia, but in a number of diseases, and found no relation between the two. He remarked that we do not know when the increased cell destruction corresponding to the hyperleucocytosis takes place, and that from the amount of uric acid in the urine we cannot tell the total amount formed.

It was in 1895 when Horbaczewski's theory was apparently confirmed by some experimenters and contradicted by others, that Krüger and Wulff[4] published a rather simple method of determining the total purin bodies of the urine. Since, outside the body the purin bases are obtained as decomposition products of nucleoproteid, it seemed possible that there might be some connection between decomposition of leucocytes and the amount of purin bases in the urine, so that within a year or two after the publication of Krüger and Wulff's method, a number of articles appeared dealing with the relation between leucocytosis and the purin bases in the urine.

Among the first articles was that of Bondzynski and Gottlieb,[5] who found that the excretion of purin bodies as a whole, that is, the bases, xanthin, hypoxanthin, guanin, and adenin, plus uric acid, is parallel with the leucocytosis. These authors believed that their work explained the contradictory results obtained by former experimenters. When there is leucocytosis and normal uric acid excretion, then the purin bases in the urine are high. When the uric acid is high, it is due to an oxidation of these purin bases. They found in their cases of leukemia normal excretion

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[1] Matthes. Zur Chemie des leukämischen Blutes. Berl. klin. Wochenschrift, Vol. 31, pp. 531 and 556 (1894).

[2] P. Jacob und M. Krüger. Ueber Harnsäure, Xanthinbasen, und Leukocyten bei einem mit Organextrakten behandelten Falle von Leukämie. Deutsche med. Wochenschrift, Vol. 20, pp. 641 and 663 (1894).

[3] P. Richter. Ueber Harnsäureausscheidung und Leukocyten. Zeitschr. für klin. Med., 27, 290 (1895).

[4] M. Krüger und C. Wulff. Ueber eine Methode zur quantitativen Bestimmung der sogenannten Xanthinkörper der Harne. Zeitschr. für physiol. Chem., 20, 176 (1895).

[5] St. Bondzynski und R. Gottlieb. Ueber Xanthinkörper im Harne eines Leukämikers. Arch. für exp. Path. u. Pharmak., 36, 127 (1895).

of uric acid, but increased excretion of purin bases. Gumprecht[1] confirmed this parallelism of the excretion of purin bases and the number of leucocytes in the blood. He, too, found normal uric acid excretion, but increased excretion of purin bases in leukemia. Kolisch and Stejskal[2] and Kolisch and Dostal[3] as a result of their work believed the excretion of purin bodies a direct expression of the decomposition of the leucocytes.

Kühnau,[4] too, found that the excretion of purin bases varies with the number of leucocytes in the blood, and was confirmed by Kühnau and Weiss.[5] Later,[6] he found that injection of blood into an animal causes an increased excretion of uric acid, proportional to the number of leucocytes in the blood injected, and expressed the view that the excretion of purin bodies is a direct measure of the leucocyte decomposition. Drabczyk,[7] as a result of work which he did, came to the same conclusion as Kühnau.

Unfortunately, all these experimenters used the method of Krüger and Wulff in their determinations of the purin bodies of the urine. Weintraud,[8] Zülzer,[9] Laquer,[10] Huppert,[11] and Salkowski[12] have shown that this method is unreliable, so that the conclusions arrived at from determination of the purin bodies in the urine by this method are valueless. Flatow and Reitzenstein[13]

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[1] Gumprecht. Alloxurkörper und Leukocyten beim Leukämiker. Centralblatt für allgem. Path. und path. Anat., 7, 820 (1896).

[2] R. Kolisch und K. Stejskal. Ueber die durch Blutzerfall bedingten Veranderungen des Harnes. Zeitschr. für klin. Med., 27, 446 (1895).

[3] R. Kolisch und H. Dostal. Das Verhalten der Alloxurkörper in pathologischen Harnen. Wiener klin. Wochenschrift, 8, 413 (1895).

[4] W. Kühnau. Experimentelle und klinische Untersuchungen über das Verhaltniss der Harnsäureausscheidung zur Leukocytose. Zeitschr. für klin. Med., 28, 534 (1895).

[5] W. Kühnau und F. Weiss. Weitere Mitteilungen zur Kenntnis der Harnsäure Ausscheidung bei Leukocytose und Hyperleukocytose sowie zur Pathologie der Leukämie. Zeitschr. für klin. Med., 32, 482 (1897).

[6] W. Kühnau. Ueber das Verhalten des Stoffwechsels und der weissen Blutelemente bei Blutdissolution. Deutsche Arch. für klin. Medizin, 58, 339 (1897).

[7] T. Drabczyk. Ueber die Methode zur Bestimmung der Harnsäure und ein Beitrag zur Theorie der Entstehung der Harnsäure. Maly's Jahresb. über die Fortschritte der Thierchemie, 26, 353 (1896).

[8] Weintraud. Beiträge zur Stoffwechsel der Gicht. Charité Annalen, 215 (1895).

[9] G. Zülzer. Ueber die Alloxurkörperausscheidung im Harne bei Nephritis. Berl. klin. Wochenschrift, 23, 72 (1896).

[10] B. Laquer. Ueber die Krüger-Wulffsche Methode der Alloxurkörperbestimmung Centralblatt für innere-Medizin, 17, 1129 (1896).

[11] H. Huppert. Ueber die Bestimmung der Xanthinbasen nach Krüger-Wulff. Zeitschr. für physiol. Chem., 22, 556 (1897).

[12] E. Salkowski. Ueber die Krüger-Wulffsche Methode zur Bestimmung der Alloxurkörper im Harne. Deutsche med. Wochenschrift 23, 213 (1897).

[13] R. Flatow und A. Reitzenstein. Zur Xanthinbasenbestimmung im Urin. Deutsche med. Wochenschrift, 23, 354 (1897).

showed that the Wulff-Krüger method gives much higher results than the Salkowski method, in fact, as much as seven times higher in some cases.

During the last few years a number of men have studied the relation of the excretion of uric acid to the number of leucocytes in the blood, and have found no relation between the two. Matthes [1] and Münzer [2] have studied the excretion of uric acid in leukemia and found it normal. Neither Pope,[3] Wey,[4] nor Stroux and Levison [5] could find any coincidence of hyperleucocytosis and high excretion of uric acid.

Zagari and Pace [6] studied carefully the relation of the number of leucocytes to the excretion of uric acid, and found that in leukemia the increase in the number of leucocytes and the increase in uric acid excretion are not parallel. They found, too, that while the increased excretion of uric acid after eating meat is much higher than after a vegetable diet, the number of leucocytes is not dependent on whether the food is animal or vegetable. They found further that spermin increases the excretion of purin bases and uric acid, but does not change the number of leucocytes.

Mayer [7] found that although the ingestion of thymus gland increases the excretion of uric acid, it does not increase the number of leucocytes. He found, also, cases where there is a low uric acid excretion and a high number of leucocytes. Camerer [8] found that while thymus does cause a slight increase in the number of leucocytes, this increase is not greater than the increase caused by ingestion of the same quantity of milk. The thymus brings about an increased excretion of uric acid, but the milk does not. Spleen nuclein was found by Jakob and Bergell [9] to cause in-

[1] M. Matthes. Zur Chemie des leukämischen Blutes. Berl. klin. Wochenschrift, 31, 531 (1894).

[2] E. Münzer. Die Bedeutung der Ammoniaksalze für die Pathologie, nebst einen Beiträge zum Stoffwechsel der Leukämie. Prager Mediz. Wochenschrift, 22, 171 (1897).

[3] C. Pope. Zur Kenntnis der Beziehungen zwischen Hyperleucocytose und Alloxurkörperausscheidung. Centralblatt für innere Medizin, 20, 657 (1899).

[4] Wey. Beiträge zur Kenntnis der Leukämie. Archiv. für klin. Med., 57, 287 (1896).

[5] Stroux und Levison. Dissert., Bonn., 1897.

[6] G. Zagari e D. Pace. La genesi dell' acido urico e la gotta in riguardo alla patogenesi e alla indirizzo terapeutico. Napoli, 1897, from Centralblatt für innere Medizin, 19, 816 (1898).

[7] P. Mayer. Ueber den Einfluss von Nuklein und Thyreoidinfütterung auf die Harnsäureausscheidung. Deutsche med. Wochenschrift, 22, 186 (1896).

[8] W. Camerer. Harnsäure, Xanthinbasen, und Phosphorsäure im menschlichen Urin. Zeitschr. für Biol., 33, 139 (1898).

[9] P. Jakob und P. Bergell. Ueber den Einfluss nukleinhaltiger Nahrung auf Blut und Stoffwechsel unter besonderer Berüchtsichtigung den Phosphorsäurestoffwechsels. Zeitschr. für klin. Med., 35, 171 (1898)

creased excretion of uric acid. There was, however, no parallel increase of the number of leucocytes.

Fåhraens[1] found that in starving persons there is as much variation in the number of leucocytes during the day as in a person who has food and has, therefore, the so-called digestive leucocytosis. Yet in starving persons the uric acid excretion is constant.[2] This would seem to indicate that there is no dependence of the uric acid excretion upon the number of leucocytes. Siven[3] found different quantities of leucocytes in the blood on different days, although the food was the same. He found, likewise, almost a constant quantity of uric acid excreted with a variable number of leucocytes.

Krüger and Schmidt[4] found that hypoxanthin increases the excretion of uric acid but does not increase the number of leucocytes in the blood. Croton oil, which, according to Weiss,[5] gives a hyperleucocytosis, does not give an increased excretion of uric acid.[5] Further, Magnus-Levy[6] studied the excretion of purin bodies and uric acid in leukemia and found no increase in the excretion of either, and Loewi[7] found no change in the relative amounts of different nitrogenous urinary constituents in leukemic urine. Henderson and Edwards[8] found the excretion of uric acid even rather low in leukemia. Melis-Schirru[9] found quite frequently an increased excretion of uric acid without a hyperleucocytosis.

Another objection that has been raised against Horbaczewski's theory is that the increase in the number of leucocytes in a

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[1] Bruhn Fåhraens. Klinische Studien über die Zahl der weissen Zellen im menschlichen Blute. Nod. med. Ark., 1897, p. 46.

[2] Schreiber und Waldvogel. Beitrag zur Kenntnis der Harnsäureausscheidung unter physiologischen und pathologischen Verhältnissen. Arch. für exp. Path. u. Pharmak., 42, 69 (1899).

[3] V. Siven. Zur Kenntnis der Harnsäurebildung im menschlichen Organismus unter physiologischen Verhältnissen. Skandinav. Archiv. f. Physiologie, 11, 123 (1901).

[4] Krüger und Schmidt. Die Entstehung der Harnsäure aus freien Purinbasen. Zeitschr. für physiol. Chem., 34, 549 (1901–1902).

[5] J. Weiss. Weitere Beiträge zur Erforschung der Bedingungen der Harnsäurebildung. Zeitschr. für physiol. Chem., 27, 216 (1899).

[6] A. Magnus-Levy. Ueber den Stoffwechsel bei akuter und chronischen Leukämie. Virchow's Archiv, 152, 107 (1898).

[7] O. Loewi. Beiträge zur Kenntnis des Nukleinstoffwechsels. 1 Mitheil. Archiv. für exp. path. u. Pharmak., 44, 1 (1900).

[8] Y. Henderson and G. Edwards. A Study of Metabolism in a Case of Lymphatic Leukemia. Am. Journ. of Physiol., 6, xxii, 1902, and Nuclein Metabolism in Lymphatic Leukemia. Am. Journ. of Physiol., 9, 417 (1903).

[9] Melis Schirru. Sulla genesi dell' acido urico. Centralblatt für innere Medizin, 20, 1042 (1899).

peripheral vessel, which was used as a measure of the number of leucocytes in the blood, does not necessarily indicate increased leucolysis, or even a general increase in the number of leucocytes throughout the blood. Rieder[1] was the first to call attention to the fact that an increase in the number of leucocytes in a peripheral vessel does not necessarily indicate increased leucolysis. Indeed, he and, later, his pupil Schulz[2] found that when the number of leucocytes in the peripheral vessels increases, there is a corresponding decrease in the number of leucocytes in the internal vessels, and that when there is a peripheral hypoleucocytosis, there is an increase in the number of leucocytes in internal vessels. They came to the conclusion that the total number of leucocytes in the body is nearly constant.

Goldscheider and Jacob[3] obtained results somewhat similar to those of Rieder and Schulz. These authors, too, showed that a decrease in the number of leucocytes in a peripheral vessel does not necessarily indicate a leucolysis, but find that in this case the capillaries of the lungs are well filled with leucocytes. They do not, however, conclude that the total number of leucocytes is constant. Richter and Spiro[4] and Bohland[5] from experimental evidence came to the same conclusion as Goldscheider and Jacob.

In explanation of the fact that sometimes a large increase in the number of leucocytes was often accompanied by only a small increase in the excretion of uric acid, and that a considerable increase in the excretion of uric acid was often accompanied in his experiments by only a slight increase in the number of leucocytes, Horbaczewski said that the quantity of the nuclei substance in different individual leucocytes is different, and that, consequently, a hyperleucocytosis of leucocytes poor in nucleoproteid would not give the same amount of uric acid on decomposition as a hyperleucocytosis of leucocytes rich in nuclear substance. Mares[6] pointed out that this explanation in itself was

[1] H. Rieder. Beiträge zur Kenntnis der Leukocytose und verwandter Zustände des Blutes, 203. Leipzig, 1892.

[2] Schulz. Experimentelle Untersuchungen über das Vorkommen und die diagnostische Bedeutung der Leukocytose. Arch. für klin. Med. 51, 234, 1893.

[3] Goldscheider und Jacob. Ueber die Variationen der Leukocytose. Zeitschr. für klin. Med., 25, 373 (1894).

[4] Richter und Spiro. Ueber die Wirkung intravenöser Zimmtsäureinjectionen auf das Blut. Archiv. für exp. Path. u. Pharmak., 34, 289 (1894).

[5] Bohland. Ueber die Einwirkung den Hidrotica und Antihidrotica auf den Leukocytengehalt des Blutes. Centralblatt für innere Medizin, 20, 361 (1899).

[6] F. Mares. Zur Theorie der Harnsäurebildung im Säugethierorganismus. Monatshefte für Chemie, 13, 101 (1892).

an objection to the theory, since Horbaczewski counted only the number of leucocytes in his experiments and did not indicate the amount of nuclear substance. Another objection that Mares brought up in the same article is that if the leucocytes are the source of uric acid, then those of the spleen, lymph, and interstitial tissue must have a very great influence on the excretion of uric acid. Horbaczewski evidently believed that the number of leucocytes in the blood alone serves as a measure of the uric acid excretion.

Weintraud [1] found that nuclein which, when taken in the food serves to increase the excretion of uric acid, does not always increase the number of leucocytes. In this respect he found that meat gives a greater hyperleucocytosis than nuclein, although it does not increase the excretion of uric acid so much. He summed the matter up saying that so long as we judge the uric acid formation by the uric acid excretion and the leucocyte decomposition by the number of leucocytes in a peripheral vessel, so long will we try in vain to prove Horbaczewski's hypothesis that the formation of uric acid is due to the decomposition of leucocytes. In regard to the first part of his statement, we now believe that there is a relation between the uric acid formation and the uric acid excretion.

The uric acid excreted cannot all come from the food, for Tuczek [2] showed long ago that it does not disappear from the urine in starvation. In this he has been confirmed by many experimenters. Then, since nucleoproteid can serve as a source for uric acid, and since the leucocytes are rich in nucleoproteid, it seems *à priori* probable that some of the uric acid excreted is derived from them. This, too, is the conclusion that Zagari and Pace [3] and Douglas [4] come to. The experimental results of Douglas in some respects contradict those of Zagari and Pace, but they both conclude that while the number of leucocytes may have some effect on the excretion of uric acid, yet this effect has been greatly overrated.

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[1] W. Weintraud. Ueber den Einfluss des Nukleins der Nahrung auf die Harnsäurebildung. Berl. klin. Wochenschrift, 32, 405 (1895).

[2] F. Tuczek. Mittheilung von Stoffwechseluntersuchungen bei abstinirenden Geisteskranken. Archiv. für Psychiatrie, 15, 784 (1884).

[3] G. Zagari e D. Pace. La genesi dell' acido urico e la gotta in riguardo alla patogenesi e alla indirizzo terapeutico. Napoli, 1897. From Centralblatt für innere Medizin, 19, 816 (1898).

[4] C. Douglas. Some Observations on the Excretion of Uric Acid with Special Reference to Its Connection with Leucocytosis. Edinburgh Med. Journ., 1900, p. 32.

Uric Acid from Cells other than the Leucocytes. — As Jakob[1] pointed out, there are nucleoproteids in the nuclei of cells other than the leucocytes that may serve as a source for uric acid. He believed that the increased excretion of uric acid in the degeneration of the liver caused by phosphorous poisoning comes from the nucleoproteid of the nuclei of the liver cells. This increased excretion of uric acid in phosphorous poisoning had been previously noted by Horbaczewski,[2] Münzer,[3] and Lieblein.[4] Nencki, Pawlow, and Zaleski[5] also noticed increased excretion of uric acid in liver degeneration, and gave it the same explanation that Jakob did. It may be noted that von Jaksch[6] has found an increase in the excretion of ammonia, urea, and amino-nitrogen, as well as uric acid in phosphorous poisoning.

Another view of the source of the uric acid from the body tissue is that of Minkowski,[7] that it may be as well due to an increased function of the cell as an increased destruction. This, too, is the view of Melis-Schirru,[8] who ascribes both hyperleucocytosis and increased excretion of uric acid to a common cause. Melis-Schirru noticed quite frequently an increased excretion of uric acid without a coincident hyperleucocytosis, but never a hyperleucocytosis without an increase in the uric acid excretion. He thinks that an increased function of the lymph organs leads to a storing up of nuclein substance in them, and this leads first to an increased excretion of uric acid and later to a hyperleucocytosis. The view that increased excretion of uric acid is connected with increased function of cells is likewise that of Mares,[9] who thinks

[1] P. Jakob. Ueber Harnsäure, Xanthinbasen, und Leucocytose bei Leukämie. Vortr. geh. in d. physiol. Gesell. zu Berlin am 13 April, 1894. Du Bois Archiv, 378 (1894).

[2] Horbaczewski. Beiträge zur Kenntnis der Bildung der Harnsäure und der Xanthinbasen sowie der Entstehung der Leukocytose im Säugethierorganismus. Monatshefte für Chemie, 12, 221 (1891).

[3] E. Münzer. Der Stoffwechsel des Menschen bei akuter Phosphorvergiftung. Deutsch. Arch. für. klin. Med., 52, 199 (1894).

[4] V. Lieblein. Die Stickstoffausscheidung nach Leberverödung beim Säugethiere. Archiv. für exp. Path. u. Pharmak., 33, 318 (1894).

[5] Nencki, Pawlow, und Zaleski. Ueber den Ammoniakgehalt des Blutes und der Organe und die Harnstoffbildung bei den Säugethieren. Arch. für exp. Path. u. Pharmak., 37, 26 (1896).

[6] R. v. Jaksch. Ueber die Verteilung des Stickstoffes im Harne bei einem Falle von Phosphorvergiftung nebst vergleichenden Beobachtungen über einige neuere Methoden der Harnstoffbestimmung. Zeitschr. für physiol. Chem., 40, 123 (1903).

[7] O. Minkowski. Ueber Leukämie und Leucocytose. Verhandl. des 17 Kongr. für innere Med., 158 (1899).

[8] Melis-Schirru. Sulla genesi dell' acido urico. Centralblatt für innere Med., 20, 1042 (1899).

[9] F. Mares. Sur l'origine de l'acide urique chez l'homme. Archives slaves de Biologie, 3, 207 (1888). Centralb. für med. Wissen., 26, 2 (1888).

that increased excretion of uric acid is brought about by increased activity of the digestive glands. He pointed out that the excretion of uric acid is constant in starvation, and that, after a proteid diet, the increased excretion begins within an hour and attains its maximum in from six to eight hours. Kam [1] has confirmed this latter fact. The uric acid excretion, therefore, is parallel with the activity of the digestive glands. Further, pilocarpin, which increases the activity of all glands, increases the excretion of uric acid.

From Muscular Activity. — Siven [2] thinks that muscular work may cause the formation of that part of the uric acid which is not derived from the food. He observed an increased excretion of uric acid after muscular exercise. A slightly increased excretion of uric acid after bodily movement had been noted by Montessier,[3] and also by Herter and Smith.[4] An increased excretion of uric acid, to the extent of from 25 to 40 per cent, had been noticed by Kolisch [5] after a snow-shoe party. Robin [6] found that although the nitrogenous metabolism as a whole increased during the muscular exercise in bicycling, the excretion of uric acid decreased. Laquer [7] and Zagari [8] found decreased excretion of uric acid during muscular work. Blake and Larrabee [9] found that the excretion of uric acid was decreased in the runners after the twenty-five mile Marathon race at Boston to a slight extent. They do not, however, give their figures or their method of determination. Accord-

[1] B. Kam. Bijdragen tot de kennis der urinezuuruitscheidung. Diss. Leiden (1898). Maly's Jahresb. über die Fortschritte der Thierchem, 28, 573 (1898).

[2] V. Siven. Zur Kenntniss der Harnsäurebildung im menschlichen Organismus unter physiologischen und pathologischen Verhältnissen. Skandinav. Archiv. f. Physiol., 11, 123 (1901).

[3] Montessier. Wien. medic. Bl., 1890, No. 32. Maly's Jahresb. über die Fortschritte der Thierchemie, 21, 182 (1892).

[4] C. Herter and E. Smith. Observations on the Excretion of Uric Acid in Health and in Disease. N. Y. Med. Journ., 1892, June 4, p. 38.

[5] Kolisch (from Laquer. Ueber die Ausscheidungsverhältnisse der Alloxurkörper im Harn von Gesunden und Kranken. Verhandl. des 14 Kongr. für innere Medizin, Wiesbaden, 333 [1893]).

[6] A. Robin. Action de l'exercise moderne à bicyclette sur l'acide urique et dans un cas d'albuminurie par sclérose rénale concomitante. Centralblatt für innere Med., 359 (1895).

[7] Laquer. Ausscheidungsverhältnisse der Alloxurkörper im Harn von Gesunden und Kranken. Verhandl. des 14 Kongr. für innere Medizin, Wiesbaden (1896), 333.

[8] G. Zagari. Influenza della inalazioni ossigeno e del moto sull' eliminazione dell' acido urico e corpi affini. Napoli (1898).

[9] J. Blake and R. Larrabee. Observations upon Long-Distance Runners. Boston Medical and Surgical Journal, Vol. 158, No. 8, 195 (1903).

ing to Sherman,[1] muscular exercise has no effect on the excretion of uric acid when the subject experimented on is in training. Neither Laval[2] nor Rockwood[3] could find any effect of muscular work on the excretion of uric acid. According to the latter, exhaustive labor causes an increase in the excretion of uric acid.

The experiments of Genth and Henle,[4] who found that exercise increases the excretion of uric acid, those of Hammond,[5] who found the excretion decreased, those of Lehmann,[6] who found it unchanged, and those of Speck,[7] who found it sometimes increased and sometimes unchanged by exercise, are of no value, for these authors used the inaccurate Heinz method for determining uric acid. As a result of a few experiments, Dunlop, Paton, Stockman, and Maccadam[8] have concuded that the excretion of uric acid is increased except when the patient is in training. The scanty data does not warrant their conclusion, however.

Burian[9] has studied the effect of muscular activity on the excretion of uric acid with more care than any other experimenters. This author found that although on days of muscular activity there is no greater excretion of uric acid than on days of rest, yet the excretion of uric acid after a few hours of muscular exercise is very much greater than after a similar period of rest. On further study of the subject, Burian found that if diluted defibrinated blood is passed through an isolated muscle, purin bases and uric acid are found in the blood on its exit from the muscle. When the muscle was stimulated to action by the electric current, more hypoxanthin and uric acid was found in the blood passing

[1] H. Sherman. On the Influence of Diet, Muscular Exertion, and Loss of Sleep upon the Formation of Uric Acid in Man. Journ. Am. Chem. Soc., 25, 1158 (1903).

[2] E. Laval. De l'influence des exercises physiques sur l'excretion de l'acide urique. Revue de Méd., 16, 384 (1896).

[3] E. Rockwood. The Elimination of Endogenous Uric Acid. Am. Journ. of Physiol. 12, 38 (1904).

[4] Henle. Handbuch der rationelle Pathologie, I, 335.

[5] Hammond. Am. Journ., Jan., 1855 (cited by Meissner. Zeitsch. für rationelle med., 31, 234, [1868]).

[6] Lehmann. Arch. für wissenschaftliche. Heilkunde 4, 484.

[7] Speck. Arch. für wissenschaftliche. Heilkunde 4, 521, and 6, 161.

[8] J. Dunlop, D. Paton, R. Stockman, and I. Maccadam. On the Influence of Muscular Exercise, Sweating, and Massage on the Metabolism. Journ. of Physiol., 22, 68 (1897).

[9] R. Burian. Die Bildung der Harnsäure im Organismus des Menschen. Med. Klinik, 1, 131 (1905).

Ibid. Die Herkunft der endogenen Harnpurine bei Mensch und Säugethier. Zeitschr. für physiol. Chem., 43, 532 (1905).

out of the muscle than when the muscle was at rest, and, further, the quantity of hypoxanthin in the muscle itself increased. As we shall see later, a very large part of the hypoxanthin introduced into the body is excreted as uric acid, so that Burian's results would indicate muscular activity as a source of uric acid. In fact, this author believes that hypoxanthin is constantly being formed as a result of muscular activity, and that this is the most important source of the endogenous uric acid excreted. This may, to some extent, explain the results of Rockwood,[1] who found the hourly excretion of uric acid greater during the day than during the night.

In regard, then, to the source of the uric acid which comes from the body tissue, we cannot at this writing give a complete statement. Burian's work seems to indicate hypoxanthin formed in muscular activity as one source. It seems probable that when cells do degenerate, the nucleoproteid of the nuclei can serve as a source for uric acid, since nucleoproteid taken in the food is known to give uric acid, so that in leukemia, and after the absorption of the exudate in pneumonia, and also after the liver degeneration caused by phosphorous poisoning, we may ascribe a cause for the increased excretion of uric acid. We have no proof as yet, however, that the physiological variations in the excretion of uric acid are due to the same cause. We can say nothing positive concerning increased cell activity as a source of uric acid. There is no definite evidence to show that this is the case. The view first proposed by Weintraud that uric acid in the urine is due in part to absorption and oxidation of purin bodies from the mucous membrane of the alimentary canal will be discussed in the section on the purin bodies of the feces. The relative importance of the uric acid derived from the body cells and that derived from the food will be discussed later.

The Nucleins and Purin Bodies of the Food as a Source of the Uric Acid and Purin Bodies Excreted. — It has been seen that there is no parallelism between the concentration of the leucocytes in the blood and the amount of uric acid excreted. We have no reason, therefore, to believe that the

[1] E. Rockwood. The Elimination of Endogenous Uric Acid. Am. Journ. of Physiol., 12, 38 (1904).

increased excretion of uric acid after feeding bodies containing nucleins is due primarily to an increased decomposition of leucocytes.

We now have abundant evidence to show that food containing nucleoproteids increases the excretion of uric acid. Only Gumlich[1] in recent times missed an increased excretion of uric acid after feeding thymus gland, and Mayer[2] after feeding spleen. Gumlich used dogs in his experiments. We shall see later that in dogs uric acid is oxidized in part to allantoin. Further, Gumlich used the inaccurate Heinz method for the determination of uric acid. This author obtained a slight increase in the extractive matter, which may be due to allantoin.

Calves' thymus was shown by Luethje[3] and Minkowski[4] to increase the excretion of uric acid in dogs. Mayer[2] and Minkowski obtained in men an increased excretion of uric acid after administration of 100 grams thymus. Rosenfeld and Orgler[5] replaced 500 grams meat by thymus in the diet and obtained a large increase in the excretion of uric acid. Weiss[6] found the uric acid excretion increased after replacing 375 grams meat by 375 grams thymus, and Weintraud[7] after administration of from 750 to 1,000 grams of calves' thymus obtained an increased excretion of uric acid for two days. Hess and Schmoll[8] gave a pretty illustration of the action of thymus. They showed that if a certain weight of yolk of egg be added to a standard diet, there is no increase in the excretion of uric acid. If, instead of yolk of egg, the same weight of thymus gland is used, an increase in the amount of uric acid excreted is noted.

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[1] G. Gumlich. Ueber die Aufnahme der Nuklein in den thierischen Organismus. Zeitschr. für physiol. Chem., 18, 508 (1894).

[2] P. Mayer. Ueber den Einfluss von Nuklein- und Thyreoidin-fütterung auf die Harnsäureausscheidung. Deutsche med. Wochenschrift, 22, 186 (1896).

[3] Luethje. Ueber Bleigicht und den Einfluss der Bleüntoxication auf die Harnsäureausscheidung. Zeitschr. für klin. Med., 29, 266 (1896).

[4] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

[5] Rosenfeld und Orgler. Zur Behandlung der harnsäuren Diathese. Centralblatt für innere Medizin, 17, 42 (1896).

[6] J. Weiss. Weitere Beiträge zur Erforschung der Bedingungen der Harnsäurebildung. Zeitschr. für physiol. Chem., 27, 216 (1899).

[7] W. Weintraud. Ueber Harnsäure im Blute. Wiener klin. Rundschau, No. 1 (1896).

[8] N. Hess und E. Schmoll. Ueber die Beziehungen der Eiweiss und Paranukleinsubstanzen der Nahrung zur Alloxurkörperausscheidung im Harne. Arch. für exp. Path. . Pharmak., 37, 243 (1896).

Mochizuchi,[1] Brandeburg,[2] Jerome,[3] Pope,[4] Weintraud,[5] Umber,[6] Camerer,[7] and Taylor,[8] all observed an increased excretion of uric acid after thymus feeding in health, while Schmoll,[9] in a gouty patient, and Zagari and Pace,[10] in patients with nephritis and leukemia, observed the same result, so that there can be no doubt that thymus nuclein at least gives an increase in the excretion of uric acid.

Increased excretion of uric acid has been obtained by Hopkins and Hope [11] after administration of herring sperm and swine sperm, and also after the administration of free spleen nuclein and yeast nuclein, by Weiss [12] and Taylor [8] after replacing meat by pancreas, by Jakob and Bergell [13] after feeding spleen nuclein to a patient, by Umber [6] after administration of liver, and by Minkowski [14] after administration of salmon sperm. Jerome [15] obtained a rise of 25 per cent in the excretion of uric acid after using 4 grams free nuclein obtained from yeast, and a rise of 75 per cent after using 10 grams of free nuclein from spleen.

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[1] J. Mochizuchi. Ueber die Resorption von Eiweisskörpern von der Schleimhaut des Dickdarmes nach Versuchen mit Thymusklystieren. Arch. für Verdauungskrankheiten, 7, 222 (1901).

[2] C. Brandeburg. Ueber die diagnostische Bedeutung der Harnsäure und Xanthinbasen im Urin. Berl. klin. Wochenschrift, 33, 137 (1896).

[3] W. Jerome. The Formation of Uric Acid in Man, and the Influence of the Diet on Its Daily Output. Journ. of Physiol., 22, 146 (1898).

[4] C. Pope. Zur Kenntniss der Beziehungen zwischen Hyperleukocytose und Alloxurkörperausscheidung. Centralblatt für innere Medizin, 20, 657 (1899).

[5] W. Weintraud. Ueber Harnsäurebildung beim Menschen. Vortrag. geh. in. d. physiol. Gesellsch. zum Berlin am 1 März, 1895. Du Bois Archiv, 382 (1895).

[6] F. Umber. Ueber den Einfluss nukleinhaltiger Nahrung auf die Harnsäurebildung. Zeitschr. für klin. Med., 29, 174 (1896).

[7] W. Camerer. Harnsäure, Xanthinbasen, und Phosphorsäure im menschlichen Urin. Zeitschr. für Biol., 33, 139 (1896).

[8] A. Taylor. The Influence of Various Diets upon the Elimination of Uric Acid and the Purin Bases. Amer. Journ. of Med. Sciences, 118, 141 (1899).

[9] E. Schmoll. Stoffwechselversuch an einem Gichtiker. Zeitschr. für klin. Med., 29, 510 (1896).

[10] G. Zagari e D. Pace. La genesi dell' acido urico e la gotta in riguardo alla patogenesi e alla indirizzo terapeutico. Napoli, 1897, from Centralblatt für innere Medizin, 19, 816 (1898).

[11] Hopkins and Hope. On the Relation of Uric Acid Excretion to Diet. Journ. of Physiol., 23, 271 (1898).

[12] J. Weiss. Weitere Beiträge zur Erforschung der Bedingungen der Harnsäurebildung. Zeitschr. für physiol. Chem., 27, 216 (1899).

[13] P. Jakob und P. Bergell. Ueber den Einfluss nukleinhaltiger Nahrung auf Blut und Stoffwechsel unter besonderer Berücksichtigung des Phosphorsäurestoffwechsels. Zeitschr. für klin. Med., 35, 171 (1898).

[14] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

[15] W. Jerome. Further Proofs of the Origin of Uric Acid from Nuclein Compounds. Journ. of Physiol. 25, 98 (1898–99).

Richter [1] found an increased excretion of uric acid for two days after feeding 10 grams of the sodium salt of nucleic acid, and Minkowski [2] obtained the same result in dogs and in men after feeding thymus nucleic acid and salmon nucleic acid. All these foodstuffs, — thymus, fish sperm, yeast, liver, pancreas, spleen, and so forth, — which have been found to increase the excretion of uric acid, are rich in nucleoproteid, and therefore in purin bases. We shall see that Burian and Schur [3] were able to show quantitatively how much uric acid can be obtained from a weighed amount of nuclein.

Since food material containing nucleins, the free nucleins themselves, and nucleic acid were found to increase the excretion of uric acid, since this increase is not caused by an intermediate decomposition of leucocytes, and since, as will be shown later, foodstuffs other than those containing purin bases do not influence the excretion of uric acid, it seemed certain from the close chemical relation between the purin bases and uric acid that increased excretion of uric acid after nuclein feeding is due to the presence of these bases, yet Nencki and Sieber [4] and Stadthagen [5] who fed xanthin to dogs, Kerner [6] who fed guanin, and Kossel [7] who fed adenin could not observe an increased excretion of uric acid. We shall see, however, that dogs do not react exactly like other animals toward purin bases. Instead of increased excretion of uric acid, we are more likely to get an increased excretion of allantoin, an oxidation product of uric acid. Minkowski [8] was the first to obtain increased excretion of uric acid

[1] P. Richter. Ueber Harnsäureausscheidung und Leucocytose. Zeitschr. für klin. Med., 27, 290 (1895).

[2] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

[3] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. I. Mitteilung. Pflüger's Archiv., 80, 241 (1900).

Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. II. Mitteilung. Pflüger's Archiv, 87, 239 (1901).

Das quantitative Verhalten der menschlichen Harnpurinausscheidung. Pflüger's Archiv, 94, 273 (1903).

[4] M. Nencki und N. Sieber. Ueber eine neue Methode, die physiologische Oxydation zu messen und über den Einfluss der Gifte und Krankheiten auf dieselbe. Pflüger's Archiv, 31, 319 (1883).

[5] Stadthagen. Ueber das Vorkommen der Harnsäure in verschiedenen tierschen Organen, ihr Verhalten bei der Leukämie und die Frage ihrer Entstehung aus den Stickstoffbasen. Virchow's Archiv, 109, 390 (1887).

[6] Kerner. Ueber das Verhalten das Guanins. Annal. d. Chem. und. Pharm., 103, 249 (1857).

[7] A. Kossel. Ueber das Adenin. Zeitschr. für physiol. Chem., 12, 241 (1888).

[8] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für. exp. Path. u. Pharmak., 41, 375 (1898).

after administration of free purin bases. He found that xanthin and hypoxanthin, but not adenin, gives increased excretion of uric acid, even in dogs. Burian and Schur [1] found that xanthin and hypoxanthin give increased excretion of uric acid in men, and Krüger and Schmidt [2] found that adenin, and to a slight extent guanin, give increased uric acid excretion.

The proof that the free purin bases increase the excretion of uric acid is very important, since it explains the relationship between the diet and the uric acid in the urine. A number of authors had maintained that the amount of uric acid excreted is dependent upon the amount of proteid in the food. Others denied any relationship between the two. Practically all authors, however, agreed that a meat diet gives more uric acid than a vegetable diet.

Only Jones [3] found no difference in the amount of uric acid excreted, whether the diet consisted chiefly of meat or of vegetables; but he employed the useless Heinz method for the determination of uric acid. Lehmann [4] found 1.0 gram uric acid excreted in twenty-four hours on a purely vegetable diet, 1.1 grams on a mixed diet, and 1.4 on a diet consisting chiefly of meat. H. Ranke [5] found .88 gram uric acid on a meat diet and only .65 gram on a vegetable diet. Haughton [6] found three times as much uric acid excreted by beef eaters as by vegetarians. Horbaczewski [7] found that the excretion of uric acid is diminished when part of the meat in the diet is replaced by sugar or fat. The results of Hermann [8] on the excretion of uric acid in twenty-four hours on different kinds of diet are .046 to .050 gram uric acid nitrogen on a vegetable diet, .060 to .075 gram on a mixed diet, and .097 to .104 gram on a meat diet. Rosenfeld and

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[1] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. I. Mitteilung. Pflüger's Archiv, 80, 241 (1900).

Ibid. II. Mitteilung. Pflüger's Archiv, 87, 239 (1901).

[2] M. Krüger und J. Schmidt. Ueber die Entstehung der Harnsäure aus freien Purinbasen. Zeitschr. für physiol. Chem., 34, 549 (1902).

[3] Jones. Philosophical Transactions, 796 (1849),

[4] Lehmann. Lehrb. d. physiol. Chem., 2d ed., Vol. I (1853).

[5] H. Ranke. Beobachtungen und Versuche über die Ausscheidung der Harnsäure bei Menschen. München (1858).

[6] S. Haughton. On the Natural Constants of the Healthy Urine of Man. The Dublin Quarterly, 28, 1 (1859).

[7] J. Horbaczewski und F. Kanera. Ueber den Einfluss von Glycerin, Zucker, und Fett auf die Ausscheidung der Harnsäure. Monatshefte für Chemie, 7, 105 (1886).

[8] A. Hermann. Ueber die Abhangigheit der Harnsäureausscheidung von Nahrungs- und Genussmitteln mit Rücksicht auf die Gicht. Deutsche Arch. für. klin. Medizin, 43, 273 (1888).

Orgler [1] found in the twenty-four hours' urine .374 to .587 gram uric acid during starvation, .576 to 1.005 grams with 600 grams meat, .756 to .776 gram with 800 grams meat, and 1.299 to 2.793 grams with 1,650 grams of meat. Dapper [2] tried several sets of experiments upon himself and upon his laboratory servant, and in all cases found a decreased excretion of uric acid when part of the meat in the food was replaced by vegetables, fats, or carbohydrates. J. Ranke,[3] Bunge,[4] Marez,[5] Schultz,[6] Schreiber and Waldvogel,[7] Taylor,[8] and Burian and Schur [9] likewise found that higher excretion of uric acid is brought about by a meat diet than by a diet of vegetables, fats, or carbohydrates, and that the amount of uric acid excreted does not bear a constant ratio to the amount of urea.

Milk, in this respect, acts like vegetable food, and when substituted for meat brings about a decrease in the excretion of uric acid. To be sure, Kussmanoff [10] did not find this to be the case, but his work is open to criticism. Markow,[11] Umber,[12] Laquer,[13] and Burian and Schur,[14] on the other hand, who did more careful work,

[1] Rosenfeld und Orgler. Zur Behandlung der Harnsäure Diathese. Centralblatt für innere Medizin, 17, 42 (1896).

[2] C. Dapper. Ueber Harnsäureausscheidung bei gesunden Menschen unter verschiedenen Ernahrungsverhältnissen. Berl. klin. Wochenschrift, 30, 619 (1893).

[3] J. Ranke. Physiol. des Menschen, 4t ed. (1881).

[4] G. Bunge. Lehrb. d. physiol. u. pathol. Chem., 1 ed., p. 291 (1887); 2d ed., p. 344.

[5] F. Marez. Sur l'origine de l'acide urique chez l'homme. Archives slaves de Biologie, 3, 207 (1888); Centralblatt für die Wissenschaftl. Med., 26, 2 (1888).

[6] E. Schultz. Ueber den Einfluss der Nahrung auf die Ausscheidung des Amidartiger Substanzen. Pflüger's Archiv, 45, 401 (1889).

[7] Schreiber und Waldvogel. Beitrag zur Kenntnis der Harnsäureausscheidung unter physiologischen und pathologischen Bedingungen. Arch. für exp. Path. u. Pharmak., 42, 69 (1899).

[8] A. Taylor. The Influence of Various Diets upon the Elimination of Uric Acid and the Purin Bases. Amer. Journ. of Med. Sciences, 118, 141 (1899).

[9] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. I. Mitteilung. Pflüger's Archiv, 80, 241 (1900).

Ibid. Das quantitative Verhalten des menschlichen Harnpurinausscheidung. Pflüger's Archiv, 94, 273 (1903).

[10] Kussmanoff. Ueber die Ausscheidung der Harnsäure bei absoluter Milchdiät. Dissert. Dorpat (1885).

[11] Markow. Zur Frage des Stickstoffumsatze bei ausschliesslicher Milchdiät. Maly's Jahresb. über die Fortschritte der Thierchemie, 18, 296 (1888).

[12] F. Umber. Ueber den Einfluss nucleinhaltiger Nahrung auf die Harnsäurebildung. Zeitschr. für klin. Med., 29, 174 (1896).

[13] B. Laquer. Ueber die Ausscheidungsverhaltnisse der Alloxurkörper im Harne von Gesunden und Kranken. Verhandl. der 14 Kongr. für innere Med., 333 (1896), Wiesbaden.

Ueber die Beeinflussung des Alloxurkörper (Harnsäure und Xanthinbasen) Ausscheidung durch Milchdiät und über Fettmilch bei Gicht. Berl. klin. Wochenschrift, 33, 807 (1896).

[14] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. I. Mitteilung. Pflüger's Archiv, 80, 241 (1900).

Ibid. Das quantitative Verhalten des menschlichen Harnpurinausscheidung. Pflüger's Archiv, 94, 273 (1903).

all found that less uric acid was excreted when part of the meat in the food is replaced by milk, and Sherman [1] found that there is no increase in the excretion of uric acid when the diet is increased by the addition of milk. Laquer [2] and Loewi [3] found that if meat is replaced by a quantity of eucasein, — prepared from casein by treatment of the latter with ammonia, — containing the same amount of nitrogen, the excretion of uric acid is lowered considerably.

It was found further that if meat is replaced by an equivalent quantity of other animal proteid material free from purins, there is a decreased excretion of uric acid. Thus Rosenfeld [4] found that a replacement of part of the meat food by aleuronat, sodium caseinate, peptone, or nutrose, resulted in a decreased excretion of uric acid. Hirschfeld [5] found that a decrease in the excretion of uric acid follows when meat is replaced by milk, vegetable proteid, or egg. Chotzen [6] obtained the same result when he replaced the meat of the food by an equivalent quantity of nutrose. Hopkins and Hope [7] found no increase in the excretion of uric acid when white of egg or milk was given to a person who had fasted for fourteen hours. Hess and Schmoll [8] observed no increase in the excretion of uric acid after yolk of egg was added to a standard diet, and Burian and Schur [9] could not observe an increased excretion of uric acid when vegetables, milk, or eggs were added to a standard diet.

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[1] H. Sherman. On the Influence of Diet, Muscular Exertion, and Loss of Sleep upon the Formation of Uric Acid in Man. Journ. Am. Chem. Soc., 25, 1159 (1903).

[2] B. Laquer. Nachtrag zu den Aussatze über Herabsetzung der Harnsäureausscheidung bei Milchdiät. Deutsche klin. Wochenschrift, 33, 853 (1896).

[3] J. Loewi. Der Eiweisstoffwechsel in einen Falle von Anemia splenica und der Einfluss des Eukasins auf denselben. Fortschritte der Medicin, 14, 689 (1896).

[4] G. Rosenfeld. Grundzüge der Behandlung der Harnsäurer Diathese. Verhandl. des 14t Kongr. für innere Med., 321, Wiesbaden (1896).

Harnsäure u. Gicht. Allgem. medicinische Centralzeitung, 65, 789 (1896).

[5] F. Hirschfeld. Beiträge zur Ernahrungslehre des Menschen. Virchow's Archiv, 114, 301 (1888).

[6] Chotzen. Inaug. Dissert. Breslau, 1897.

[7] F. Hopkins and W. Hope. On the Relation of Uric Acid to Diet. Journ. of Physiol., 23. 271 (1898).

[8] N. Hess und E. Schmoll. Ueber die Beziehungen der Eiwiess- und Paranukleinsubstanzen der Nahrung zur Alloxurkörperausscheidung im Harne. Arch. für. exp. Path. u. Pharmak., 37, 243 (1896).

[9] Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. I. Mitteilung. Pflüger's Archiv, 80, 241 (1900).

Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. II. Mitteilung. 87, 239 (1901).

Pfeil,[1] too, has shown that food free from purin bodies does not affect the excretion of uric acid. This author showed that there is an increase in the rate of excretion of uric acid within two hours after changing from a meat-free to a meat diet.

If, as we now believe, the influence of foodstuffs on the excretion of uric acid is dependent entirely, or nearly so, on their content in purin bodies, we should not expect the amount of uric acid in the urine to stand in a constant ratio with the total nitrogen, as Haig maintains. It will not be necessary to call attention to the numerous experiments directly showing this, for almost any set of experiments on different persons that we can pick out will show it. Busquet's[2] experiment is interesting. He kept a patient on a limited diet for a year and a half to decrease his weight. The patient lost 32.5 kilos, and the urea excretion decreased from 28 to 10 grams per day, yet the excretion of uric acid remained stationary at about .6 gram per day. When the urea is very low, the uric acid may be slightly decreased, too, according to Folin.[3]

Experiments during the last half dozen years have shown that it is the meat extract consisting of constituents of the meat which are soluble in water that gives the increased excretion of uric acid. Strauss[4] found that 50 grams of meat extract gave an increase of 50 per cent in the excretion of uric acid in one series of experiments, and 91 per cent in another series. Jerome[5] observed a similar effect after the use of Liebig's extract. He administered in one case 10 grams and in another 40 grams, and after both observed a rise in the excretion of uric acid, — a rise of 50 per cent after the 40 grams. Zagari and Pace[6] and also Siven[7]

[1] P. Pfeil. Ueber den Einfluss der Nahrungsaufnahme auf die Ausscheidung der Harnsäure. Zeitschr. für physiol. Chem., 40, 1, 1903.

[2] G. Busquet. Etude de quelque phénomènes urologiques constatés dans une observation d'obésité avec hernie de la ligne blanche guérie par un traitement hygiénique rationel. Revue de médecine, 12, 572 (1892).

[3] O. Folin. Laws Governing the Chemical Composition of Urine. Am. Journ. of Physiol., 13, 66 (1905).

[4] H. Strauss. Ueber die Beeinflussung der Harnsäure und Alloxurbasenausscheidung durch die Extractstoff des Fleisches. Berl. klin. Wochenschrift, 33, 710 (1896).

[5] W. Jerome. The Formation of Uric Acid in Man, and the Influence of Diet on Its Daily Output. Journ. of Physiol., 22, 146 (1898). *Also*, Further Proofs of the Origin of Uric Acid from Nuclein Compounds. Journ. of Physiol. 25, 98 (1898–99).

[6] G. Zagari e D. Pace. La genesi dell' acido urico e la gotta in riguardo alla patogenesi e all' indirizzo terapeutico. Napoli, 1897; Centralblatt für innere Med., 19, 816 (1898).

[7] V. Siven. Zur Kenntnis der Harnsäurebildung im menschlichen Organismus unter physiologischen Verhaltnissen. Skandinav. Archiv. f. Physiol., 11, 123 (1900).

confirmed these experiments with Liebig's meat extract. Siven [1] found that meat extract causes an increased excretion of uric acid, and that the meat itself, after the meat extract had been separated from it, does not give an increased excretion.

The small quantity of nucleoproteid found in meat could not, as Brandeburg [2] protested, account for the effect of meat in increasing the excretion of uric acid. We have seen that meat does contain free purin bases, especially hypoxanthin, but it was not until Minkowski [3] showed that free hypoxanthin and xanthin can increase the excretion of uric acid when taken in the food that we could definitely attribute the effect of meat on the uric acid excretion to the free purin bodies contained in it. Burian and Schur [4] have shown that the quantity of purin bases in meat is sufficient to account for the difference in the amount of uric acid excreted on a meat diet and on a diet free from meat.

According to Klemperer,[5] fish, like meat, causes increased excretion of uric acid.

It seems plain, then, that meat and glandular organs rich in cells give an increase in the excretion of uric acid by virtue of the content of these foodstuffs in purin bases, either free or combined. The bases are to some extent oxidized to uric acid in the body. The detailed consideration of the oxidation of the individual purin bodies and the relative importance of the uric acid derived from the purin bodies of the food will be discussed later.

The Relative Quantity of Uric Acid from the Food and that from the Body Tissues. — We see, then, that the purin bodies and those compounds from which purin bodies can be obtained by hydrolytic splitting can serve as a source for uric acid in the mammal organism. On the other hand, it has been

[1] V. Siven. Zur Kenntnis der Harnsäurebildung im menschlichen Organismus unter physiologischen Verhaltnissen. Skandinav. Archiv. f. Physiol., 11, 123 (1901).

[2] C. Brandeburg. Ueber die diagnostiche Bedeutung der Harnsäure und Xanthinbasen im Urin. Berl. klin. Wochenschrift 33, 137 (1896).

[3] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. und Pharmak., 41, 375 (1898).

[4] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. Pflüger's Archiv, 80, 241 (1900).

[5] G. Klemperer. Ist Fischkort rathsamer als Fleisch bei harnsäurer Diathese und Nephritis. Therapie der Gegenwart, Neue Folge II, 428 (1901).

shown by Schreiber and Waldvogel,[1] Tuczek,[2] Lo Monaco,[3] and others that in man, at any rate, uric acid is excreted during starvation, and by Cario [4] and by von Noorden [5] that the excretion is increased in inanition so that we can come to the view first expressed by Camerer,[6] that the uric acid excreted comes from two sources, — the food and the body cells. Wiener [7] has shown that in the dog practically no uric acid is excreted in the urine unless purin bodies, nuclein, or nucleoproteids are given in the food.

The Endogenous Uric Acid. — Since it has become firmly established that some of the uric acid excreted by man comes from the food and some from the body tissues, attempts have been made to determine what proportion of the uric acid comes from each source. Camerer[6] believed that we cannot tell how much of the uric acid comes from the food and how much from the tissues. He thinks it probable that purin bodies are found in all nitrogenous food, and, further, that if we did find food free from purin bodies and feed a patient upon it, some of the uric acid excreted at that time might be derived from purin bodies eaten a few days before but not oxidized immediately and excreted.[8] Schreiber and Waldvogel [1] determined the uric acid excreted by two men who starved for three days. On the third day they found .197 and .205 grams respectively. They assumed that the amount of uric acid excreted during starvation represents that which comes normally from the body, and concluded from their two experiments that the amount of uric acid derived from the body tissues is constant, not dependent on the individual, and is approximately .20 gram per day. Since, on the same

[1] Schreiber und Waldvogel. Beitrag zur Kenntnis der Harnsäureausscheidung unter physiologischen und pathologischen Verhältnissen. Arch. für exp. Path. u. Pharmak., 42, 69 (1899).

[2] F. Tuczek. Mitteilung v. Stoffw. Untersuch. b. Geisteskranken. Medicin. Centralblatt (1885).

[3] Lo Monaco. Bollet della Societ. Lancis. degli de Roma, Vol. 14, parte 2, p. 102 (1894). Cited by Burian and Schur. Pflüger's Archiv, 80, 241 (1900).

[4] Cario. Ueber d. Einfluss d. Fiebers und d. Inanition auf d. Ausscheidung d. Harnsäure. Göttingen, 37 (1888).

[5] von Noorden. Lehrbuch der Pathologie des Stoffwechsels, 168.

[6] W. Camerer. Harnsäure, Xanthinbasen, und Phosphorsäure im menschlichen Urin. Zeitschr. für Biol., 33, 139 (1896).

[7] H. Wiener. Ueber synthetische Bildung der Harnsäure im Tierkörper. Beiträge zur chemischen Physiologie und Pathologie, 2, 42 (1902).

[8] W. Camerer. Beitrag zur Erforschung der Stickstoffhaltigen Bestandtheile des menschlichen Urins insbesondere der Sogennanten Alloxurkörper. Zeitschr. für Biol., 35, 206 (1897).

food, different individuals excrete different amounts of uric acid, they concluded that the amount of uric acid derived from the food depends not only on the food, but also on the individual.

Burian and Schur [1] carried out a series of experiments in which they determined the "endogenous" uric acid of the urine and the "exogenous," as they call respectively the uric acid coming from the body cells and the uric acid coming from the food. These authors maintain that the uric acid excreted during starvation cannot be considered, as Schreiber and Waldvogel consider it, the endogenous uric acid. Starvation is not a physiological condition. Lo Monaco [2] found that the professional faster Succi excreted .250 gram uric acid on the twenty-fifth day of starvation, an amount greater than Schreiber and Waldvogel found. Further, Ranke [3] and Hofmann [4] found more uric acid excreted during use of a diet free from purin bodies than during starvation. According to Burian and Schur [1] the endogenous uric acid may be considered equal to the amount excreted when the patient is fully nourished, but receives in his food no purin bodies, either free or combined. The value of the endogenous uric acid determined in this way is different for different individuals, but constant at different times for the same individual if he does not considerably change his mode of life. The exogenous uric acid, on the other hand, is, according to them, dependent solely on the amount and kind of purin bodies in the food. It is not different for different individuals if they eat the same kind and quantity of food.

These authors found that by changing the diet from one consisting of milk, cheese, and eggs, high in proteid, to a milk-cheese-eggs diet low in proteid, and then to a vegetable diet there is no change in the amount of uric acid excreted. Hall [5] found that if the amount of proteid in a diet free from purin bodies kept constant, but the value in calories per day be consid-

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[1] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. I. Mitteilung. Pflüger's Archiv, 80, 241 (1900).

[2] Lo Monaco. Bollet della Societ. Lancis. degli de Roma, Vol. 14, parte 2, p. 102 (1894). Cited by Burian and Schur.

[3] J. Ranke. Kohlenstoff- und Stickstoff-ausscheidung des ruhenden Menschen. Arch. f. Anat. u. Physiol., 301 (1862).

[4] K. Hoffman. Lehrb. d. Zoochemie, 446, Wien (1879).

[5] W. Hall. The Purin Bodies of Food Stuffs. Inaug. Dissert., Owens College, Manchester, Eng. (1902).

erably changed, the amount of uric acid in the urine remains constant. According to Hirschfeld's results,[1] the value in calories of the food and the amount of proteid in the food may both be changed without influencing the amount of uric acid excreted. Hall[2] and Rockwood,[3] too, found that the amount of purin bodies in the urine is independent of the quantity of proteid and of the heat value of the food. The uric acid excreted seems to be independent of the quality and the quantity of the food within wide limits, so long as the food is free from purin bodies. According to Folin,[4] the endogenous uric acid is not absolutely constant in any individual. When the total nitrogen excretion is exceedingly low, the endogenous uric acid is somewhat decreased.

In a series of experiments on Burian in May, 1899, lasting twenty days, Burian and Schur[5] found an average quantity of .199 gram endogenous purin nitrogen in the urine per day. In a series of experiments in November, 1899, lasting four days, the average amount of purin nitrogen excreted was .200 gram. In a third series, in December, 1900, lasting nine days, .199 gram per day was the average amount of purin nitrogen excreted. Siven[6] likewise found the endogenous uric acid in the urine individually constant and independent of the food.

In experiments on five different people Burian and Schur found, respectively, .203, .153, .122, .155, and .137 grams endogenous uric acid per day. They pointed out experiments of Hirschfeld,[1] Herringham and Davies,[7] Camerer,[8] Schreiber and Waldvogel,[9] and

[1] F. Hirschfeld. Beiträge zur Ernährungslehre des Menschen. Virchow's Archiv, 114, 301 (1888).

[2] I. W. Hall. The Purin Bodies of Food Stuffs. Inaug. Dissert, Owens College, Manchester, Eng. (1902).

[3] E. Rockwood. The Elimination of Endogenous Uric Acid. Am. Journ. of Physiol. 12, 38, 1904.

[4] O. Folin. Laws Governing the Chemical Composition of Urine. Am. Journ. of Physiol., 13, 66 (1905).

[5] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. 1. Mitteilung. Pflüger's Archiv, 80, 241 (1900).

[6] V. Siven (3). Zur Kenntnis der Harnsäurebildung im menschlichen Organismus unter physiologischen Verhaltnisse. Skandinav. Archiv. f. Physiol., 11, 123 (1901).

[7] W. Herringham and H. Davies. On the Excretion of Uric Acid and Urea. Journ. of Physiol., 12, 475 (1891).

[8] W. Camerer. Gesammtstickstoff, Harnstoff, Harnsäure, und Xanthinkörper im menschlichen Urin. Zeitschr. für Biol., 28, 72 (1891).

[9] Schreiber und Waldvogel. Beitrag zur Kenntnis der Harnsäureausscheidung unter physiologischen und pathologischen Verhältnissen. Arch. für exp. Path. u. Pharmak., 42, 69 (1899).

Minkowski,[1] in which the endogenous uric acid was, respectively, .153 gram, .200 gram, .132 gram, .145 gram, and .075 gram. Rockwood,[2] too, found the endogenous uric acid different for different individuals. From these results we can see that the endogenous uric acid is different for different individuals.

It might be well to state at this point that Burian and Schur determined both the uric acid and the total purin bodies of the urine. In drawing their conclusions they speak chiefly of the purin bodies as a whole. All their conclusions concerning the endogenous purin nitrogen, however, apply equally well to the endogenous uric acid, as can be seen from their tables. It is well to speak of this point, for although the purin bodies of the urine make up but a very small fraction of the total amount of purin bodies, yet we know that purin bases are found in the feces as well. Then, again, His and Hagen[3] have criticized the accuracy of all the methods so far recommended for the determination of purin bases. These objections do not apply to the conclusions concerning uric acid, however.

Loewi[4] concluded from two series of experiments which he performed that both the endogenous and exogenous uric acid excreted are dependent entirely upon the amount of purin bodies absorbed from the food. He assumed, however, that the amount of P_2O_5 excreted is a measure of the nuclein and purin bodies absorbed. In his two series of experiments he did find the ratio $\frac{\text{uric acid}}{P_2O_5}$ approximately the same. The uric acid in the two series varied considerably, however, and in fact, Burian and Schur were able to use the results as confirmation of their own conclusions. We have seen that the excretion of phosphoric acid is not a measure of the nuclein absorbed.

In a second article,[5] Loewi criticized Burian and Schur for calling the uric acid excreted during use of a diet containing milk wholly

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[1] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

[2] E. Rockwood. The elimination of endogenous uric acid. Am. Journ. of Physiol., 12, 38 (1904).

[3] W. His und W. Hagen. Kritische Untersuchungen über den Nachweis von Harnsäure und Purinbasen im Blut, und in thierischen Organen. Zeitschr. für physiol. Chem., 30, 350 (1900).

[4] O. Loewi. Beiträge zur Kenntnis der Nukleinstoffwechsel. I. Mitteilung. Archiv. für exp. Path. u. Pharmak., 44, 1 (1901).

[5] *Ibid.* Untersuchungen über den Nukleinstoffwechsel. II. Mitteilung. Archiv. für Exp. Path. u. Pharmak., 45, 157 (1901).

endogenous, since these authors themselves [1] have found that the amount of nucleoproteid increases in sucklings as they grow older, although they obtain nothing but milk as food. This is not an objection against the conclusions of Burian and Schur regarding the endogenous uric acid, for milk does not give a greater excretion of uric acid than any other food not containing purin bodies. The uric acid derived from the nucleoproteid synthesized during use of a milk diet is truly endogenous.

Another criticism of Loewi is that the endogenous uric acid as determined by Burian and Schur is a "starvation value," comparable with the "starvation value" of NaCl or nitrogen. We know that when NaCl is withheld from the food, some NaCl is excreted in the urine. This is derived from the body tissues, but is greater than the amount ordinarily derived from the tissues. The organism tries to make up for the poverty of the food in NaCl. In NaCl or proteid starvation we know that in a short time sickness and death result. This is not the case when purin bodies are withheld from the food. Sucklings excrete very large quantities of uric acid on a diet free from purin material. Burian and Schur [2] in a recent article answer Loewi's objection and say that we cannot consider a diet such as one free from purin bodies which maintains a person in good health for an indefinitely long period in any sense a "starvation diet."

A principal difference between the endogenous uric acid and the endogenous proteids and inorganic salts used up is that the nucleoproteid of the body cells, which is probably the source of the endogenous uric acid, can be synthesized from material free from purin bodies. Thus Tichomiroff [3] found by analyis of fresh-laid eggs of certain insects (Bombyx Mori. L.) less than 0.02 per cent of hypoxanthin and guanin, and no xanthin. After these eggs had partly developed by standing through the winter, he found 0.13 per cent hypoxanthin and guanin and 0.10 per cent xanthin. These purin bodies were in the cell nuclein. In the nuclein of fresh-laid hen's eggs (pseudonuclein) Kossel [4] could

[1] Burian und Schur. Ueber Nukleinbildung im Säugethierorganismus. Zeitschr. für physiol. Chem., 23, 55 (1897).

[2] *Ibid.* Das quantitative Verhalten der menschlichen Harnpurinausscheidung. Pflüger's Archiv, 94, 273 (1903).

[3] A. Tichomiroff. Chemische Studien über die Entwicklung der Insekteneier. Zeitschr. für physiol. Chem., 9, 518 (1885).

[4] A. Kossel. Weitere Beiträge zur Chemie des Zellkernes. Zeitschr. für physiol. Chem., 10, 248 (1886).

find no purin bodies. After fifteen days' incubation he found 0.28 per cent guanin and 0.66 per cent hypoxanthin. Real nucleoproteid had been formed from compounds free from purin bodies. Burian and Schur[1] performed a series of experiments in which they determined the amount of purin bodies and real nuclein in newborn rabbits and puppies, and again in animals of about the same weight and from the same litter after they had lived on milk for a few weeks. It was found in all cases that there was a very great increase in the quantity of nuclein. From these results we can see that nucleoproteid can be synthesized in the animal organism from material free from purin bodies.

The last objection brought up by Loewi against the statements of Burian and Schur is that they are not justified in "schematizing" physiological processes as they have done. This objection Loewi applied especially to the statements of Burian and Schur concerning the exogenous uric acid, which we will take up next. Burian and Schur, however, have maintained that they merely stated observed facts and did not offer any hypotheses.[2]

Siven[3] has likewise found the endogenous uric acid constant for any one person and independent of the food.

Uric Acid from the Purin Bodies of the Food. — We have seen that some of the uric acid excreted is derived from the purin bodies of the food. In dogs, Wiener[4] has shown that this is the source of practically all the uric acid in the urine. Burian and Schur[5] have shown that, in man, the exogenous uric acid depends solely on what purin bodies are present in the food and their quantity. A certain fraction of the xanthin administered, for example, appears in the urine as uric acid. A certain other fraction of the adenin administered appears as uric acid. The fraction of each purin body which appears in the urine as uric acid is practically the same for all persons. Minkowski[6] had come to the

[1] R. Burian und H. Schur. Ueber Nukleinbildung im Säugethierorganismus. Zeitschr. für physiol. Chem., 23, 55 (1897).

[2] *Ibid.* Das quantitative Verhalten der menschlichen Harnpurinausscheidung. Pflüger's Archiv, 94, 273 (1903).

[3] V. Siven. Zur Kenntnis der Harnsäurebildung im menschlichen Organismus unter physiologischen Verhaltnissen. Skandinav. Archiv. für Physiol., 11, 123 (1901).

[4] H. Wiener. Ueber synthetische Bildung der Harnsäure im Thierkörper. Beiträge zur chemischen Physiologie und Pathologie, 2, 42 (1902).

[5] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. I. Mitteilung. Pflüger's Archiv, 80, 241 (1900).

[6] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Archiv. für exp. Path. und Pharmak., 41, 375 (1898).

conclusion that formation of uric acid from purin bodies depended on whether these bodies were free, or combined loosely, or firmly in the nucleins and nucleoproteids. He took this stand because his experiments seemed to show that adenin does not become oxidized to uric acid in the organism when administered as free adenin, whereas it is well known that the adenin combined in the nucleoproteid of calves' thymus does become oxidized to uric acid. Burian and Schur [1] showed that in the case of hypoxanthin, at any rate, the same fraction of hypoxanthin is oxidized to uric acid in the body whether it is administered in the free condition or combined as nucleic acid, nuclein, and nucleoproteid.

Before considering the quantitative experiments of Burian and Schur and others on the behavior of the individual purin bodies in the organism, it will be well to say a word in regard to the absorption of nucleoproteids, nucleins, nucleic acid, and the purins, and the occurrence of these substances in the feces.

Absorption of Nuclein and Purin Bodies

Direct experiment by Popoff [2] showed that nuclein is absorbed in large part in the small intestine. In Gumlich's [3] experiments, nuclein was absorbed, for he found it in the chyme. Bokay [4] alone stated that nuclein is not absorbed. He based his statement on the fact that he found nuclein in the feces. Since, as we shall see, nuclein in the feces may be derived from the body tissue itself, Bokay's conclusions are of no value. The experiments of Burian and Schur [1] seem to indicate that xanthin and hypoxanthin, free or combined, are practically completely absorbed. These authors found that the same fraction of these bodies is changed to uric acid in the organism, whether the base is free or combined and within wide limits, whether large or small amounts are administered.

Hall [5] found 50 per cent of the guanin taken per os in the feces.

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[1] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. I. Mitteilung. Pflüger's Archiv, 80, 241 (1900).

[2] P. Popoff. Ueber die Einwirkung von eiweissverdauenden Fermenten auf die Nucleïnstoffe. Zeitschr. für physiol. Chem., 18, 533 (1894).

[3] Gumlich. Ueber die Aufnahme der Nucleïne in den thierischen Organismus. Zeitschr. für physiol. Chem., 18, 508 (1894).

[4] A. Bokay. Ueber die Verdaulichkeit des Nucleins und Lecithin. Zeitschr. für physiol. Chem., 1, 157 (1877).

[5] I. Hall. The Purin Bodies of Food Stuffs. 2d ed., Manchester, Eng., 1903.

Xanthin, thymus, and nucleic acid cause but a slight increase in the purin bodies of the feces. Hypoxanthin seems to be completely absorbed.

Salkowski [1] found that in dogs a variable part, in one case 20 per cent, in another nearly 50 per cent, of the uric acid administered per os is absorbed. Some is excreted as allantoin, some as urea. In rabbits more than half is absorbed. This is mostly excreted as urea. A small part is excreted unchanged. Salkowski fed the animal on a diet in which the nitrogen and sulphur were constant. An addition of uric acid to the food gave an increase in the nitrogen in the urine. Determinations of sulphur in the urine showed that the decomposition of body proteid was constant. The increased nitrogen in the urine was a measure of the absorption of uric acid according to Salkowski.

The Purin Bodies of the Feces

Weintraud [2] was the first to study the purin bodies of the feces. This author found from .100 to .500 gram of purin bodies per day, free or combined, in nuclein in human feces. The average quantity was .130 gram.[2] Since these purin bodies are found in the feces, even when the food contains no purin bodies, and even in the meconium of the newborn,[3] Weintraud expressed the view that they come from the mucous membrane of the alimentary canal.[4] These purin bodies do not come from bile, for they are found in feces free from bile. Petrén [5] has confirmed this fact, and further, according to Schittenhelm,[6] bile is free from purin bodies. In leukemia, when there is increased excretion of uric acid, there is likewise an increased quantity of purin bodies in the feces, according to Weintraud. Schittenhelm [6] could not confirm this. Since nuclein or purin bodies given by the mouth or by the rectum are absorbed

[1] E. Salkowski. Ueber das Verhalten in der Magen eingeführten Harnsäure im Organismus. Arch. f. exp. Path. u. Pharmak., 35, 495 (1900).

[2] W. Weintraud. Zur Enstehung der Harnsäure im Säugethiereorganismus. Verhandl. des 14 Kongr. für innere Med., 190 (1896), Wiesbaden, and Wiener klin. Rundschau (1896), No. 1, 2.

[3] *Ibid.* Beiträge zum Stoffwechsel der Gicht. Charité Annalen, 275 (1895).

[4] *Ibid.* Ueber Harnsäurebildung beim menschen. Vortrag. geh. in der physiol. Gesellsch. zu Berlin, Marz, 1895, and Du Bois Archiv, 382 (1895).

[5] K. Petrén. Nachtrag zur Mitteilung über das Vorkommen der Xanthinbasen in den Fäces. Skandinav. Archiv für Physiol., 9, 412 (1899).

[6] A. Schittenhelm. Die Purinkörper der Fäces nebst Untersuchungen über die Purinbasen der Darmwand, der Galle und des Pankreassaftes. Arch. für klin. Med., 81, 423 (1904).

and excreted as uric acid, Weintraud thinks these nucleins and purin bodies come from the intestinal membranes and serve as the source of the endogenous uric acid, for after feeding calves' thymus he could not find an increased quantity of xanthin bases in the feces.[1] Weintraud states that in infants' feces, in which oxidation processes are found, corresponding to the presence of biliverdin (oxidized bilirubin), there is chiefly uric acid and almost no purin bases. In adults' feces, on the other hand, where we have hydrobilirubin (reduced bilirubin), practically all purin bodies are present as bases and only in traces as uric acid. When calomel is administered, however, we get in adults' feces an oxidation to biliverdin and uric acid. The work of Weintraud was soon confirmed by Brandeburg,[2] who agreed with Weintraud in his conclusions.

Petrén[3] found about .15 per cent of purin bases in dry feces. This was 1.8 per cent of the total nitrogen, and is more than is in the urine. These purin bases do not come from the food, for they are found in feces when a person lives on a milk diet free from nuclein and purin bodies. According to Hall,[4] there is from .01 to .03 gram of purin nitrogen in the feces for one day. Schittenhelm[5] states that the quantity of purin bodies varies from .027 to .285 gram per day.

Micko[6] found nuclein in the feces. Ury[7] likewise found nuclein to the extent of one third of one per cent. Parker[8] states that there are no free purin bases in the feces, only those combined in nucleins. In this he was at first confirmed by Hall,[9] but more recently Hall[10] has stated that guanin and adenin may

[1] Weintraud. Ueber die Ausscheidung von Harnsäure und Xanthinbasen durch die Fäces. Centralblatt für innere Med., 16, 433 (1895).

[2] C. Brandeburg. Ueber die diagnostische Bedeutung der Harnsäure und Xanthinbasen in Urin. Berl. klin. Wochenschrift, 33, 137 (1896).

[3] K. Petrén. Ueber das Vorkommen, die Menge, und die Abstammung der Xanthinbasen in den Fäces. Skandinav. Archiv. für Physiol., 8, 315 (1898).

[4] I. Hall. A Contribution to the Knowledge of the Purin Bodies of Human Feces in Health and Disease. Journ. of Path. and Bact., 9, 246 (1904).

[5] A. Schittenhelm. Die Purinkörper der Fäces nebst Untersuchungen über die Purinbasen der Darmwand, der Galle, und der Pankreassaft. Archiv für klin. Med., 81, 423 (1904).

[6] K. Micko. Vergleichende Untersuchungen über die bei Plasmon und Fleischnahrung ausgeschiedenen Kote. Zeitschr. für Biol., 39, 430 (1900).

[7] H. Ury. Zur Methodik der Fäkaluntersuchungen. Deutsche med. Wochenschrift, 27, 718 (1901).

[8] W. Parker. The Occurrence and Origin of the Xanthin in the Feces. Am. Journ. of Physiol., 4, 83 (1901).

[9] I. Hall. The Purin Bodies of Food Stuffs. 2d ed., Manchester, Eng., 1903.

[10] *Ibid.* A Contribution to the Knowledge of the Purin Bodies of the Feces in Health and Disease. Journ. of Path. and Bact., 9, 246 (1904).

exist free in the feces. According to Schittenhelm, the purin is formed in the feces, both free and combined in nuclein and nucleic acid, the free purin bodies making up from one third to one fourth of the total quantity.

Krüger and Schittenhelm [1] found in forty-two days' feces 2.363 grams guanin, 1.88 grams adenin, .112 gram xanthin, and .300 gram hypoxanthin, an average of .11 gram of purin bases per day. Galdi [2] studied the excretion of uric acid and the purin bases in the urine and feces in leukemia. The results of these authors are not comparable, for they used different methods of determination. It has been a question whether any of the methods used by these authors for the determination of purin bases in feces are accurately quantitative.[3] Further, it is probable that the aminopurins change to oxypurins under the influence of the bacteria of the feces, so that the relative proportion of the different individual purin bodies is not important.

According to Schmidt and Strassburger,[4] about a third of the dry substance of feces is composed of bacteria, and since nuclein has been found in bacteria by Ruppel,[5] Galeoth,[6] Bendix,[7] and indeed by Schittenhelm and Tollens [8] to such an extent that the purin bodies account for about 33 per cent of the total nitrogen of the bacteria, one source of the purin bodies of the feces is established. Schittenhelm [9] maintains that the purins of the bacteria make up a considerable portion of the total purin nitrogen of the feces.

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[1] M. Krüger und A. Schittenhelm. Die Purinkörper der menschlichen Faeces. Zeitschr. für physiol. Chem., 35, 153 (1902).

[2] F. Galdi. Ueber die Alloxurkörper im Stoffwechsel bei Leukämie. Arch. für exp. Path. u. Pharmak., 49, 213 (1903).

[3] W. His und W. Hagen. Kritische Untersuchungen über den Nachweis von Harnsäure und Purinbasen im Blut und in thierischen Organen. Zeitschr. für physiol. Chem., 30, 350 (1900).

[4] Schmidt und Strassburger. Die Fäces des Menschen. Berlin, 1903.

[5] W. Ruppel. Zur Chemie der Tuberkelbazillus. Zeitschr. für physiol. Chem., 26, 218 (1899).

[6] G. Galeoth. Beiträge zur Kenntnis der bakterillen Nukleoproteid. Zeitschr. für physiol. Chem., 25, 48 (1898).

[7] E. Bendix. Zur Chemie der Bakterien. Deutsche med. Wochenschrift, 27, 18 (1901).

[8] A. Schittenhelm und C. Tollens. Untersuchungen über den quantitativen Anteil der Bakterien an Stickstoff und Purinbasen des Fäces. Zentralbl. für innere Medizin, 25, 761 (1904).

[9] A. Schittenhelm. Die Purinkörper der Fäces nebst Untersuchungen über die Purinkörper der Darmwand, der Galle, und des Pankreassaftes. Arch. für klin. Med., 81, 423 (1904).

Hall [1] studied the effect of diet on the quantity of purin in the feces. The greatest quantity was found on a vegetable diet, the least on a milk diet. Parker [2] found a greater quantity of purin bases in the feces on a meat diet than on a diet of milk or carbohydrates. According to Schittenhelm,[3] the oxypurins, xanthin, and hypoxanthin, and meat, which contains hypoxanthin, do not cause an increase in the quantity of purins in the feces when taken in the food, but thymus gland, which contains the aminopurin adenin, does increase the quantity of purins in the feces. Schittenhelm's results were confirmed by Hall,[1] who showed that meat and hypoxanthin, unless taken in excessive quantities, do not affect the quantity of purins in the feces, but that thymus gland, or guanin, or pancreas which contains guanin, taken in the food do increase the quantity of purins in the feces. In fact, in some cases as much as 60 per cent of the guanin eaten was found again in the feces.

Hall [4] noted that in diarrhœa and inflammatory conditions of the digestive tracts, the quantity of purin bases in the feces is increased. Schittenhelm,[3] too, found the purin bases in the feces high in diarrhœa and low, on the other hand, in cases of constipation and disease of the pancreas. In the latter case he attributes the result to poor digestion of the nucleoproteids of the food.

In this connection it may be stated that Araki [5] has found a nucleic acid in the mucous membrane of the small intestine, and that Schittenhelm [3] has found adenin and guanin together with smaller quantities of xanthin and hypoxanthin in the walls of the alimentary canal.

It is possible that the purin bodies in the feces may be in part simply excretion products, and that the quantity in the feces and

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[1] I. Hall. The Purin Bodies of Human Feces in Health and Disease. Brit. Med. Journ., 2, 582 (1903).

Ibid. The Purin Bodies of Food Stuffs. 2d ed., Manchester, Eng. (1903).

Ibid. A Contribution to the Knowledge of the Purin Bodies of Human Feces. Journ. of Path. and Bact., 9, 246 (1904).

[2] W. Parker. The Occurrence and Origin of the Xanthin in the Feces. Amer. Journ. of Physiol., 4, 83 (1901).

[3] A. Schittenhelm. Die Purinkörper der Fäces nebst Untersuchungen über die Purinbasen der Darmwand, der Galle, und des Pankreassaftes. Arch. für klin. Med., 81, 423 (1904).

[4] I. Hall. A Contribution to the Knowledge of the Purin Bodies of Human Feces in Health and Disease. Journ. of Path. and Bact., 9, 246 (1904).

[5] T. Araki. Ueber die Nucleinsäure aus der Schleimhaut des Dunndarms. Zeitschr. für physiol. Chem., 36, 98 (1903).

urine may be dependent both on the same antecedent cause. It is known, for example, that calcium salts are normally excreted into the intestines to some extent, and Bernard and Barreswill [1] have found that after kidney extirpation, when the urea is in the blood, it becomes partially excreted into the intestines. There is no increased excretion of uric acid into the intestines after kidney extirpation.[2] In this case, however, the purin bodies may be destroyed.

It may be mentioned too, that Schittenhelm [3] has found that the quantity of purin bases in feces decreases very much on standing, and on account of the high content of feces in bacteria, and the fact that bacteria found in the feces will decompose the purin bases from yeast nuclein,[4] this author attributed the decrease in purin bases in feces to bacterial decomposition.

To summarize briefly, we may say that the purin bodies of the feces come in large part to the nucleoproteids in the bacteria. A variable part, dependent on the kind of food eaten, but generally a small part, may come from the purin bodies of the food. Another source of importance is probably the mucous membrane lining the intestines, some of which containing purin bodies is probably thrown off and passes into the feces. There is no positive evidence that any purin bodies are excreted into the feces.

The Metabolism of the Individual Purin Bodies in the Organism.

Hypoxanthin. — We have seen that experiments by Nencki and Sieber,[5] Krüger and Salomon,[6] Baginsky,[7] and Jaffé,[8] who attempted to obtain increased excretion of uric acid by feeding hypoxanthin, gave negative results. To be sure, Strauss [9]

[1] Bernard et Barreswill. Arch. de Médecine (4e ser.), t. 13, p. 449 (1847).

[2] R. Burian und H. Schur. Über die Stellung der Purinkörper im menschlichen Stoffwechsel. Pflüger's Archiv, II. Mitteilung 87, 239 (1901).

[3] A Schittenhelm. Die Nucleinbasen der Fæces unter dem einfluss anhaltenden Fäulnis. Zeitschr. für physiol. Chem., 39, 199 (1903).

[4] A. Schittenhelm und F. Schröter. Ueber die Spalting der Hefenucleinsäure durch Bakterien. Zeitschr. für physiol. Chem., 39, 203 (1903).

[5] M. Nencki und N. Sieber. Ueber eine neue Methode, die physiologische Oxydation zu messen und über den Einfluss der Gifte und Krankheiten auf dieselbe. Pflüger's Archiv, 31, 319 (1883).

[6] M. Krüger und G. Salomon. Die Konstitution des Heteroxanthins und seine physiologische Wirkung. Zeitschr. für physiol. Chem., 21, 169 (1895).

[7] A. Baginsky. Ueber das Vorkommen von Xanthin, Guanin, und Hypoxanthin. Zeitschr. für physiol. Chem., 8, 395 (1883).

[8] Jaffé (cited by W. v. Mach. Ueber die Bildung der Harnsäure aus dem Hypoxanthin. Arch. für exp. Path. u. Pharmak., 24, 389 [1888]).

[9] H. Strauss. Ueber die Beeinflussung der Harnsäure und Alloxurkörperausscheidung durch die Extraktstoff des Fleisches. Berl. klin. Wochenschrift, 33, 710 (1896).

had attributed the increased excretion of uric acid after eating meat and meat extract to hypoxanthin. But Minkowski [1] was the first to obtain positive results by feeding the free base. In dogs he found about 4 per cent, and in men about half the hypoxanthin given excreted as uric acid. He found, however, an increase in the allantoin in the dogs equivalent to 77 per cent of the hypoxanthin given. This probably explains the origin of the allantoin observed by Meissner [2] in the urine of dogs and cats after meat eating.

Burian and Schur [3] then took up the work. These authors found that about half the hypoxanthin administered is excreted as uric acid, whether free or combined, as it is sometimes found in foodstuffs. They give the following list of their own experiments and the experiments of others.[4] The first column gives the name of the experimenter, the second the food given, and the third shows what per cent of the hypoxanthin in the food was excreted as uric acid. Galdi [5] likewise found that about one half the free hypoxanthin administered appears in the urine as uric acid.

Minkowski,[1]	hypoxanthin,	48.6
Burian and Schur,[3]	,,	46.2
Krüger and Schmidt,[6]	,,	62.3
Burian and Schur,[3]	beef,	51.1
,, ,, ,,	veal,	53.9
,, ,, ,,	ham,	63.2
Hall,[7]	chicken,	52.1
,,	fish,	58.2
,,	beef,	47.0
Kaufman and Mohr,[8]	veal,	51.6
,, ,, ,,	beef,	48.1
,, ,, ,,	.....	85.3
,, ,, ,,	.....	77.0

[1] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

[2] G. Meissner. Beiträge zur Kenntnis des Stoffwechsels im thierischen Organismus. Zeitschr. für rationnelle Med., 31, 234 (1868).

[3] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. I. Mitteilung. Pflüger's Archiv., 80, 241 (1900).

[4] *Ibid.* Das quantitative Verhalten der menschlichen harnpurinausscheidung. Pflüger's Archiv, 94, 273 (1903).

[5] F. Galdi. Ueber die Alloxurkörper im Stoffwechsel, bei Leukämie. Arch. für exp. Path. u. Pharmak., 49, 213 (1903).

[6] M. Krüger und J. Schmidt. Ueber die Entstehung der Harnsäure aus freien Purinbasen. Zeitschr. für physiol. Chem., 34, 549 (1902).

[7] I. Hall. The Purin Bodies of Food Stuffs. Inaug. Dissert., Owens College, Manchester, Eng., 1902.

Ibid. The Relation of Purin Bodies to Certain Metabolic Disorders. Brit. Med. Journ., June 14, 1902.

[8] M. Kaufmann und L. Mohr. Beiträge zur Alloxurkörperfrage und zur Pathologie der Gicht. Deutsche Arch. für klin. Medizin, 74, 141 (1902).

Burian and Schur think that the individuality plays no part in determining the amount of purin bodies of the food which are excreted as uric acid in the organism. The variations found in the different experiments are so slight that they can be due to slight errors. The results of the last two experiments in the table, they think, are due to some unexplained error. In fact, the patients used were sick.

Krüger and Schmidt[1] and Kaufmann and Mohr[2] think the variations in the results of the different experiments indicate individual variations in the amount of exogenous hypoxanthin changed to uric acid.

Burian and Schur[3] found that in different animals the amount of uric acid derived from a definite amount of hypoxanthin is diferent. In one race of dogs, for example, he found 12 per cent of the hypoxanthin injected excreted as uric acid, in another race, only 4 per cent. In rabbits, about 18 per cent of the hypoxanthin injected appears as uric acid. In cats about one twentieth to one thirtieth of the uric acid injected is excreted as uric acid.

Xanthin. — Nencki and Sieber[4] could not observe an increased excretion of uric acid after feeding the free base xanthin to dogs. Krüger and Salomon[5] likewise obtained negative results on feeding xanthin to rabbits. Burian and Schur[6] performed one experiment on man and found an increased excretion of uric acid corresponding to about 30 per cent of the xanthin fed. On analyzing the feces they found xanthin present, which they supposed was due to lack of absorption. After subtracting this from the amount given in the food, they found that the uric acid in the urine corresponded to about 43.5 per cent of the xanthin absorbed. They found, too, that of the combined hypoxanthin and xanthin in the liver, about 52 per cent was excreted as uric acid in the

[1] M. Krüger und J. Schmidt. Ueber die Entstehung der Harnsäure aus freien Purinbasen. Zeitschr. für physiol. Chem., 34, 549 (1902).

[2] M. Kaufmann und L. Mohr. Beiträge zur Alloxurkörperfrage und zur Pathologie der Gicht. Deutsche Arch. für klin. Medizin, 74, 141 (1902).

[3] Burian and Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. II. Mitteilung. Pflüger's Archiv, 87, 239 (1901).

[4] M. Nencki und N. Sieber. Ueber eine neue Methode, die physiologische Oxydation zu messen und über den Einfluss der Gifte und Krankheiten auf dieselbe. Pflüger's Archiv, 31, 319 (1883).

[5] A. Salomon. Ueber das Vorkommen von Xanthin, und Hypoxanthin. Zeitschr. für physiol. Chem., 8, 395 (1883).

[6] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. I. Mitteilung. Pflüger's Archiv, 80, 241 (1900).

urine. Burian and Schur concluded that xanthin acts quantitatively like hypoxanthin, that is to say, of the xanthin administered, whether free or combined, about half appears in the urine as uric acid. Krüger and Schmidt,[1] however, found in an experiment on a man that only 10 per cent of the uric acid administered appeared in the urine as uric acid.

Adenin. — A great many authors, as we have seen, have shown that nucleoproteid containing adenin, for example, thymus nucleoproteid, brings about increased excretion of uric acid when fed to an animal. Burian and Schur[2] showed that when thymus is taken as food, from 22 to 28 per cent of the adenin in its nucleoproteid is excreted as uric acid. Thymus nucleic acid (adenylic acid) also increases the excretion of uric acid in dogs, according to Minkowski[3] and Schittenhelm.[4]

After feeding the free base adenin to dogs, however, Minkowski[3] did not find an increased excretion of uric acid or of the purin bases in the urine. The adenin brought about inflammation of the walls of the intestine, vomiting, albuminuria, casts, and leucocytes in the urine and crystalline concretions in the kidneys. These crystalline concretions had the microscopic appearance and gave the chemical tests for uric acid. They had the same microscopical appearance as those observed in the kidney by Heidenham,[5] Damsch,[6] Ebstein and Nicolaier.[7] Nicolaier[8] gave subcutaneous injections of adenin to rats and obtained concretions in their kidneys identical with those obtained by Minkowski. He noticed, however, that, unlike uric acid crystals, these crystals dissolve in hydrochloric acid. By quantitative analysis Nicolaier showed in fact that these crystals are 6-amino-2-8-dioxypurin or dioxyadenin.

[1] M. Krüger und J. Schmidt. Ueber die Entstehung der Harnsäure aus freien Purinbasen. Zeitschr. für physiol. Chem., 34, 549 (1902).

[2] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. Pflüger's Archiv, 80, 241 (1900).

[3] O. Minkowski. Untersuchungen zur Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

[4] A. Schittenhelm und E. Bendix. Ueber das Schicksal der in der Blutbahn eingebrachten Nukleinsäure. Deutsche med. Wochenschrift, 30, 1164 (1904).

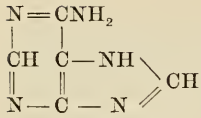
[5] R. Heidenham. Versuche über den Vorgang der Harnabsonderung. Pflüger's Archiv, 9, 23 (1874).

[6] Ebstein. Natur und Behandlung der Gicht, 78. Wiesbaden, 1882.

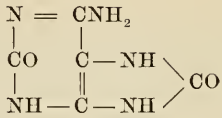
Ibid. Natur und Behandlung der Harnsteine, 77. Wiesbaden, 1884.

[7] Ebstein und Nicolaier. Ueber die Ausscheidung der Harnsäure durch die Nieren. Virchow's Archiv, 143, 337 (1898).

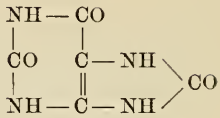
[8] Nicolaier. Ueber die Umwandlung des Adenins im Thierischen Organismus. Zeitschr. für klin. Medizin, 45, 359 (1902).



adenin



dioxyadenin



uric acid

Schittenhelm[1] found that small doses of adenin have no effect on rabbits. After large doses, concretions similar to those found in dogs are found in the kidneys. In neither case is there an increase in the excretion of uric acid. Krüger and Schmidt[2] found that if the free base adenin be fed to man, about 41 per cent is oxidized and excreted as uric acid. This is a larger fraction even than that obtained by Burian and Schur from the adenin combined in thymus. We see that adenin, like hypoxanthin, acts differently in different mammals. Krüger[3] has since shown that this increased excretion of uric acid is real and not due to an increase in the quantity of chemically similar 6-amino-2-6-dioxypurin, as had been suggested. Thus, while thymus feeding increases the excretion of uric acid in man, Cohn,[4] Minkowski,[5] and Burian and Schur[6] observed very little increased excretion of uric acid in dogs, and Mendel and Brown[7] in cats, but a very marked increase in the excretion of allantoin, which is a decomposition product of uric acid.

Guanin. — Weiss,[8] Hess and Schmoll,[9] and Loewi[10] observed increased uric acid excretion in man after pancreas feeding. Experiments with the free base guanin, which is the purin base

[1] A. Schittenhelm. Das Verhalten von Adenin und Guanin im tierischen Organismus. Arch. für exp. Path. u. Pharmak., 47, 432 (1902).

[2] M. Krüger und J. Schmidt. Ueber die Entstehung der Harnsäure aus freien Purinbasen. Zeitschr. für physiol. Chem., 34, 549 (1902).

[3] M. Krüger. Ueber die Umwandlung der Purinkörper im Organismus. Deutsche med. Wochenschrift, 29, 741 (1903).

[4] T. Cohn. Beiträge zur Kenntniss des Stoffwechsels nach Thymusnahrung. Zeitschr. für physiol. Chem., 25, 507 (1898).

[5] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

[6] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. II. Mitteilung. Pflüger's Archiv, 87, 239 (1901).

[7] L. Mendel and E. Brown. Observations on the Nitrogenous Metabolism of the Cat, Especially on the Excretion of Uric Acid and Allantoin. Am. Journ. of Physiol., 3, 261 (1900).

[8] J. Weiss. Weitere Beiträge zur Erforschung der Bedingungen der Harnsäurebildung. Zeitschr. für physiol. Chem., 27, 216 (1899).

[9] N. Hess und E. Schmoll. Ueber die Beziehungen der Eiweiss und Paranukleinsubstanzen der Nahrung zur Alloxurkörperausscheidung im Harne. Arch. für exp. Path. u. Pharmak., 37, 243 (1896).

[10] Loewi. Untersuchungen über den Nukleinstoffwechsel. II. Mitteilung. Arch. für exp. Path. u. Pharmak., 45, 157 (1901).

of pancreas nucleoproteid, on rabbits by Kerner,[1] on dogs by Stadthagen,[2] and on man by Burian and Schur [3] and Milroy and Malcolm [4] gave negative results. In dogs, Salkowski [5] found increased allantoin after pancreas feeding instead of increased uric acid. Mendel and Brown[6] observed the same effect in cats, although there was likewise a slightly increased excretion of uric acid. Schittenhelm [7] found no increased uric acid after feeding guanin to rabbits, and found no concretions in the kidneys such as were noticed after adenin feeding. He found, however, that the uric acid excretion was increased when the guanin was introduced subcutaneously or intravenously.[8] Krüger and Schmidt [9] performed one experiment on a man in which a very small amount of free guanin was given. A very slightly increased excretion of uric acid was noticed.

According to Hall,[10] guanin is poorly absorbed. Fifty per cent of the guanin fed is found again in the feces.

Before leaving the subject of the influence of these four bases on the excretion of uric acid, it may be well to state by way of summary that although the oxidation of hypoxanthin and the hypoxanthin in nuclein and nucleoproteid is to some extent clear, yet the results obtained by a study of the metabolism of the other three bases, xanthin, adenin, and guanin, by different authors are contradictory. It has not even been decided conclusively whether it makes a difference if the bases are administered free or combined in nucleoproteid. A few more experiments ought to clear up the subject. It seems clear that the metabolism of these bases is different in different mammals.

[1] A. Kerner. Ueber das Verhalten des Guanins. Liebig's Ann. der Chem. u. Pharm., 103, 249 (1857).

[2] Stadthagen. Ueber das Vorkommen der Harnsäure in verscheidenen thierischen Organen, ihr Verhalten bei der Leukämie und die Frage ihrer Entstehung aus den Stickstoffbasen. Virchow's Archiv, 109, 390 (1887).

[3] Burian und Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. I. Mitteilung. Pflüger's Archiv, 80, 241 (1900).

[4] T. Milroy and J. Malcolm. The Metabolism of the Nucleins under Physiological and Pathological Conditions. Journ. of Physiol., 23, 217 (1899).

[5] E. Salkowski. Ueber das Vorkommen von Allantoin im Harn nach Fütterung mit Pankreas. Centralbl. für med. Wissenschaften, 36, 929 (1898).

[6] L. Mendel and E. Brown. Observations on the Nitrogenous Metabolism of the Cat, Especially on the Excretion of Uric Acid and Allantoin. Am. Journ. of Physiol., 3, 261 (1900).

[7] A. Schittenhelm. Das Verhalten von Adenin und Guanin im tierschen Organismus. Arch. für exp. Path. u. Pharmak., 47, 432 (1902).

[8] A. Schittenhelm und E. Bendix. Um die Umwandlung des Guanins im Organismus des Kaninchens. Zeitschr. für physiol. Chem., 43, 365 (1905).

[9] Krüger und Schmidt. Ueber die Entstehung der Harnsäure aus freien Purinbasen. Zeitschr. für physiol. Chem., 34, 549 (1902).

[10] I. Hall. The Purin Bodies of Food Stuffs. Second ed. Manchester, Eng., 1903.

Uric Acid. — Frerichs and Wöhler[1] found no increased excretion of uric acid in rabbits after ingestion of urates, or in dogs by feeding them uric acid. Neubauer[2] found that the uric acid given to rabbits is excreted as urea. Zabelin[3] and Meissner,[4] who tried experiments on dogs, and Mendel and Brown,[5] who used cats, found that the uric acid ingested is not excreted as such. Burian and Schur,[6] however, observed in dogs and cats that about one twentieth to one thirtieth of the uric acid ingested is excreted unchanged. Thus, in dogs and cats, hypoxanthin, the adenin in thymus, and uric acid, in equal doses, give the same quantity of uric acid in the urine. Poduschka[7] noticed a very slight increase in the excretion of uric acid by dogs after ingestion of sodium urate.

In man the conclusions are slightly different. After eating 7.5 grams uric acid in one day, Stokvis[8] observed no increase in the excretion of uric acid. Stadthagen[9] ate 5 grams sodium urate and found that apparently none of it appeared again as such in the urine. The fact that uric acid administered per os does not reappear in the urine has been confirmed by Weintraud,[10] Weiss,[11] Schreiber and Waldvogel,[12] and Loewi.[13] Only

[1] F. Frerichs und F. Wöhler. Ueber die Veranderungen, welche namentlich organische Stoffe bei ihrem Ubergang in den Harn erleiden. Liebig's Ann. der Chem. u. Pharm., 65, 335 (1848).

[2] C. Neubauer. Ueber die Zersetzung der Harnsäure im Tierkörper. Liebig's Ann. der Chem. u. Pharm., 99, 206 (1856).

[3] Zabelin. Ueber die Umwandlung der Harnsäure im Thierkörper. Liebig's Ann. der Chem. u. Pharm., Suppl., 2, 326 (1863).

[4] G. Meissner. Beiträge zur Kenntniss des Stoffwechsels im tierischen Organismus. Zeitschr. für rationelle Med., III. Reihe, 31, 234 (1868).

[5] L. Mendel and E. Brown. Observations on the Nitrogenous Metabolism of the Cat. Especially on the Excretion of Uric Acid and Allantoin. Am. Journ. of Physiol., 3, 261 (1900).

[6] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. 2. Mitteilung. Pflüger's Archiv, 87, 239 (1901).

[7] Poduschka. Quantitative Versuche über Allantoinausscheidung. Arch. für exp. Path. u. Pharmak., 44, 59 (1900).

[8] Stokvis. Arch. f. d. holl. Beiträge 2, Serie 2, 260 (1860). Cited by Burian and Schur.

[9] Stadthagen. Ueber das Vorkommen des Harnsäure in verscheidenen thierischen Organen, ihr Verhalten bei Leukämie, und die Frage ihrer Entstehung aus den Stickstoffbasen. Virchow's Archiv, 109, 390 (1887).

[10] Weintraud. Ueber Harnsäure im Blute und ihre Bedeutung für die Entstehung der Gicht. Centralblatt für innere Medizin, 17, 752 (1896), and Wiener klin. Rundschau, 1896, Nos. 1 and 2.

[11] J. Weiss. Weitere Beiträge zur Erforschung der Bedingungen der Harnsäurebildung. Zeitschr. für physiol. Chem., 27, 216 (1899).

[12] Schreiber und Waldvogel. Beiträge zur Kenntnis der Harnsäureausscheidung unter physiologischen und pathologischen Verhaltnissen. Arch. für exp. Path. u. Pharmak., 42, 69 (1899).

[13] O. Loewi. Beiträge zur Kenntnis des Nukleinstoffwechsel. 1. Mitteilung. Arch. für exp. Path. u. Pharmak., 44, 1 (1901).

Donogány[1] and Haig[2] find that administration of uric acid per os in man gives increased excretion of uric acid.

Burian and Schur[3] have found that about 48 per cent of the uric acid injected subcutaneously into a man reappears unchanged in the urine. About the same fraction of the hypoxanthin eaten is excreted as uric acid. Soetbeer and Ibrahim[4] found that uric acid taken into the stomach does not increase the excretion of uric acid, probably, according to them, because it is only slightly absorbed, but found that uric acid administered by intravenous injection appears almost quantitatively in the urine. Soetbeer and Ibrahim performed but two experiments to determine the effect of uric acid injections. During the second experiment the patient became sick, so that the quantitative conclusions which they drew are not above criticism. The work of His,[5] Freudweiler,[6] and Ebstein and Nicolaier[7] has some bearing on this point. These authors found that when uric acid is injected into rabbits and men it causes inflammation, precipitates out to some extent, and is not fully absorbed for some time.

Weintraud[8] suggested that the reason that uric acid corresponding to only a part of the purin bases in the food appears in the urine is that a certain fraction of the bases is oxidized directly to urea. Only that part of the bases which reaches the place in the body where an oxidation to uric acid takes place is changed to uric acid. According to Burian and Schur,[3] however, about one half of the hypoxanthin or xanthin administered appears as uric acid in the urine, and about one half of the uric

[1] Donogány. Ueber Ausnutzung einige Nahrungs im Darmkanal. Zeitschr. für Biol., 15, 115, and Rubner. Lehrb. d. Hygiene V. Aufl., p. 532.

[2] A. Haig. Does Uric Acid Taken by Mouth increase the Excretion of that Substance in the Urine? Journ. of Physiol., 15, 167 (1894).

[3] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. 2. Mitteilung. Pflüger's Archiv, 87, 239 (1901).

[4] F. Soetbeer und J. Ibrahim. Ueber das Schicksal eingeführter Harnsäure im menschlichen organismus. Zeitschr. für physiol. Chem., 35, 1 (1902).

[5] W. His. Schicksal und Wirkungen des sauren harnsäuren Natrons in Bauch- und Gelenkhöhle des Kaninchens. Deutsche Arch. für klin. Medizin, 67, 81 (1900).

[6] M. Freudweiler. Experimentelle Untersuchungen über das Wesen der Gichtknoten. Deutsche Arch. für klin. Medizin, 63, 266 (1899).

[7] W. Ebstein und A. Nicolaier. Ueber die Ausscheidung der Harnsäure durch die Nieren. Virchow's Archiv, 147, 337 (1896).

[8] W. Weintraud. Ueber die Einfluss des Nukleins der Nahrung auf die Harnsäureausscheidung. Berl. klin. Wochenschrift, 32, 405 (1895).

Ibid. Ueber Harnsäurebildung beim Menschen. Vortrag gehalten in der physiol. Gesellsch. zu. Berl. am 1 März, 1895. DuBois Archiv, 382 (1895).

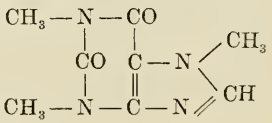
Ibid. Ueber Harnsäure im Blute und ihre Bedeutung für die Entstehung der Gicht. Wiener klin. Rundschau, No. 1, 1896, und Centralblatt für innere Medizin, 17, 752 (1896).

acid injected appears unchanged in the urine. This would seem to indicate that hypoxanthin and xanthin are oxidized almost wholly to uric acid, and then about half this uric acid is destroyed. In the case of adenin, where only about a fourth appears as uric acid in the urine, it seems probable that only one half the adenin is changed to uric acid.

We can see, then, that in regard to the behavior of the oxy- and amino-purins in the organism there is much yet to learn. We know that in man the uric acid excreted comes from two sources, — the body tissue and the nucleoproteid and purin bases of the food. The amount which comes from the body tissue is different for different individuals, but approximately constant for the same individual at different times under like conditions. Of the hypoxanthin administered, whether free or combined in nucleoproteid, about one half is excreted as uric acid. Further experiment is needed before we can state with certainty how much of the xanthin, adenin, and guanin administered is excreted as uric acid. It is not certain, either, whether or not it makes a difference if the adenin and guanin are free or combined, as in nucleoproteid. Perhaps there is a difference in the absorption. The work of Burian and Schur seems to indicate that a large part of the uric acid injected intravenously is excreted unchanged. Numerous experiments show that uric acid administered by the mouth is destroyed in the organisms, if we assume that it is absorbed, but this is an unproved assumption. In dogs, cats, and rabbits a much smaller part of the oxy- and amino-purins administered appears in the urine as uric acid than in man. In dogs and cats the uric acid is apparently further oxidized to allantoin.

The Methyl Purins. — The influence of caffein and theobromin on the excretion of uric acid is of importance on account of the occurrence of caffein in coffee and tea and the occurrence of theobromin in cocoa.

Caffein (1-3-7-*Trimethyl*-2-6-*Dioxypurin*). —



Before the relation of caffein to the other purin bodies was understood, practically nothing was known concerning its metabolism in the body. Neither Lehmann[1] nor Hammersten[2] found caffein in the urine after giving it in the food. Aubert[3] found caffein in the urine after coffee drinking. Schutzenkwer[4] obtained a qualitative test for caffein in the urine of dogs after feeding 4.8 grams of caffein to them. Maly and Andreasch,[5] after administration of .1 gram of caffein, found 66 per cent of it unchanged in the urine. Rost[6] found from 1 to 8 per cent of the caffein administered unchanged in the urine. Albanese[7] found only traces of caffein in the urine of dogs fed with caffein for a month. He found considerable quantities of a monomethylxanthin. Bondzynski and Gottlieb[8] found a methylxanthin in the urine after feeding caffein to dogs, which they later[9] identified as heteroxanthin (7-methylxanthin). Albanese[10] has since shown that the monomethylxanthin found in dogs' urine after caffein is not heteroxanthin, but 3-methylxanthin.

In rabbits, Schutzenkwer[4] found after administration of .2 gram caffein, 6 per cent unchanged in the urine. Rost[6] found from 11 to 21 per cent unchanged in the urine. Bondzynski and Gottlieb[11] found a monomethylxanthin in the urine after feeding caffein to rabbits, which they later identified as heteroxanthin 7-methylxanthin.

Albanese[7] found in the urine after feeding caffein to rabbits a little unchanged caffein, a little xanthin, but no monomethyl-

[1] Lehmann. Lehrbuch der physiol. Chem., vol 2, 367 (1850).

[2] Hammersten. N. Jahrb. Pharm., xxxv (1871).

[3] H. Aubert. Ueber Coffeingehalt des Kaffeegetrankes und über die Wirkungen des Coffeins. Pflüger's Archiv, 5, 589 (1872).

[4] Schutzenkwer. Das Coffein und sein Verhalten im Thierkörper. Inaug. Dissert., Königsberg (1882).

[5] Maly und Andreasch. Studien über Coffein und Theobromin. Monatshefte für Chemie. iv, 393 (1883).

[6] Rost. Ueber die Ausscheidung des Coffeins und der Theobromins in der Harn. Arch. für exp. Path. u. Pharmak., 36, 56 (1895).

[7] M. Albanese. Ueber das Verhalten des Caffeins und des Theobromins im Organismus. Arch. für exp. Path. u. Pharmak., 35, 449 (1895).

[8] S. Bondzynski und R. Gottlieb. Ueber Methylxanthin ein Stoffwechselprodukt des Theobromins und Coffeins. Arch. für. exp. Path. u. Pharmak., 36, 45 (1895), und Ber der Dtsch. chem. Gesell., 28, 1113 (1895).

[9] *Ibid.* Ueber die konstitution der nach Caffeins und Theobromin im Harne auftretenden Methylxanthins. Arch. für exp. Path. u. Pharmak., 37, 385 (1896).

[10] M. Albanese. Ueber die Bildung von 3-Methylxanthin aus Coffein im thierischen Organismus. Ber. der. Dtsch. chem. Gesell., 32, 2280 (1899).

[11] S. Bondzynski und R. Gottlieb. Ueber Methylxanthin ein Stoffwechselprodukt des Theobromins und Coffeins. Arch. für exp. Path. u. Pharmak, 36, 45 (1895).

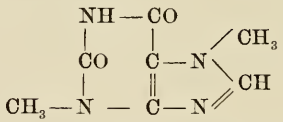
Ibid. Ber. der Dtsch. chem. Gesell., 28, 1113 (1895).

xanthin. Krüger [1] found in rabbits' urine after feeding caffein 1-7-dimethylxanthin, 1-methylxanthin, and 7-methylxanthin, but only a trace of 3-methylxanthin.

In cats, according to Schneider,[2] the greater part of the caffein administered is destroyed. According to Rost,[3] from traces up to 2.4 per cent of the amount of caffein administered is excreted unchanged in cats.

In men, no caffein could be found in the urine after coffee drinking by Dragendorff,[4] or after caffein eating by Schneider.[2] Rost [3] found only about ½ per cent of the caffein administered unchanged in the urine. Albanese [5] found xanthin in human urine after use of tea and coffee in the food, but no caffein or monomethylxanthin. After caffein feeding he obtained dimethylxanthin and some caffein in the urine.

Theobromin (3-7-*Dimethylxanthin*). —



Lehmann [6] found that theobromin administered does not reappear in the urine, but did not specify upon what animal the experiments were performed. Rost[3] found that from 10 to 32 per cent of the theobromin administered to dogs reappears in the urine. Bondzynski and Gottlieb[7] found monomethylxanthin in dogs' urine after administration of theobromin. Albanese[5] found 2 grams of monomethylxanthin in dogs' urine after administration of 10 grams in the food. Krüger and Schmidt [8] found after administration of 100 grams theobromin,

[1] M. Krüger. Ueber den Abban des Caffeins im Organismus des Kaninchens. Ber. der Dtsch. chem. Gesell., 32, 3336 (1899).

[2] Schneider. Ueber das Schicksal des Caffeins und Theobromins im Thierkörper. Inaug. Dissert. Dorpat. (1884).

[3] Rost. Ueber die Ausscheidung des Coffeins und der Theobromins in der Harn. Arch. für exp. Path. u. Pharmak., 36, 56 (1895).

[4] Dragendorff. Beiträge zur gerichtlichen Chem., 108 (1871).

[5] M. Albanese. Ueber das Verhalten des Coffeins und des Theobromins im Organismus. Arch. für exp. Path. u. Pharmak., 35, 449 (1895).

[6] Lehmann. Lehrbuch. der physiol. Chem., vol. 2, 367 (1850).

[7] S. Bondzynski und R. Gottlieb. Ueber Methylxanthin ein Stoffwechselprodukt der Theobromins und Caffeins. Arch. für exp. Path. u. Pharmak., 36, 45 (1895), und Ber. der Dtsch. chem. Gesell., 28, 1113 (1895).

[8] M. Krüger und P. Schmidt. Ueber das Verhalten von Theobromin, Paraxanthin, und 3-Methylxanthin im Organismus. Ber. der Dtsch. chem. Gesell., 32, 2677 (1899).

51 grams unchanged theobromin, .63 gram of 7-methylxanthin, and 2.9 grams of 3-methylxanthin in the urine of dogs.

In rabbits, Rost[1] found 4 to 28 per cent of the theobromin administered unchanged again in the urine. Bondzynski and Gottlieb obtained monomethylxanthin after administration of theobromin to rabbits,[2] and found 19 per cent of the theobromin administered unchanged in the urine, and 25 per cent as a monomethylxanthin.[3] Krüger and Schmidt[4] found that of 100 grams theobromin administered to rabbits, 16 grams appeared unchanged, 14 grams as 7-methylxanthin, and .9 gram as 3-methylxanthin. Hofmann[5] found theobromin in human urine after administration of diuretin a double salt of theobromin and salicylic acid.

Rost found 18 to 20 per cent of the theobromin administered to men unchanged in the urine. Bondzynski and Gottlieb[2] found a monomethylxanthin in human urine after feeding theobromin.

Other Methyl Purins. — Krüger and Schmidt[6] found after administration of theophyllin (1-3-dimethylxanthin) to a dog, 17.7 per cent unchanged in the urine and 17.9 per cent as 3-methylxanthin.

After administration of 12 grams of paraxanthin (1-7-dimethylxanthin) to a rabbit,[4] these same authors found .9 gram in the urine unchanged, and .14 gram as 1-methylxanthin.

Minkowski[7] found that 7-methyladenin is excreted in large part unchanged when administered to dogs.

Effect of the Methyl Purins on Uric Acid Excretion. — In dogs, Schutzenkwer[8] did not observe any effect of caffein on the uric acid excretion. This was confirmed by Minkowski,[7] who

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[1] Rost. Ueber die Ausscheidung des Coffeins und der Theobromins in der Harn. Arch. für exp. Path. u. Pharmak., 36, 56 (1895).

[2] S. Bondzynski und R. Gottlieb. Ueber Methylxanthin ein Stoffwechselprodukt des Theobromins und Caffeins. Ber. der Dtsch. chem. Gesell., 28, 1113 (1895).

[3] *Ibid.* Methylxanthin ein Stoffwechselprodukt des Theobromins und Caffein. Arch. für exp. Path. u. Pharmak., 36, 45 (1895).

[4] M. Krüger und P. Schmidt. Ueber das Verhalten von Theobromin, Paraxanthin, und 3-Methylxanthin im Organismus. Ber. der Dtsch. chem. Gesell., 32, 2677 (1899).

[5] A. Hofmann. Ueber die therapeutisch Anwendung des Diuretin (theobromin-natrium-natriumsalicylate). Arch. für exp. Path. u. Pharmak., 28, 1 (1891).

[6] M. Krüger und J. Schmidt. Der Abbau des Theophyllins 1-3-Dimethylxanthins im Organismus des Hundes. Zeitschr. für physiol. Chem., 36, 1 (1902).

[7] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

[8] Schutzenkwer. Das Caffein und sein Verhalten im Thierkörper. Inaug. Dissert., Königsberg (1882).

observed likewise no increase in the excretion of uric acid after feeding to dogs 7-methyladenin. After administration of 9-methyladenin, however, there was a slight increase in the excretion of uric acid.

In man, Haig,[1] whose results, as we have already seen, are open to criticism on account of the inaccurate method of determination, and on account of the fact that he refers to the ratio *uric acid* : *urea*, found increased uric acid after coffee drinking. Taylor,[2] after coffee drinking, and Hess and Schmoll,[3] after tea and cocoa drinking, likewise observed a very slight increase in the excretion of uric acid.

Leven,[4] whose method of analysis, however, was inaccurate, found no effect of coffee on the excretion of uric acid. Zagari and Pace[5] found no increased excretion of uric acid, but an increased excretion of purin bases after caffein. Burian and Schur[6] found that coffee has no effect on the excretion of uric acid. Of the purin base in coffee, about 35 to 40 per cent appears as purin bases again in the urine.

It will be seen, then, that the methyl groups of the methylpurins are gradually oxidized off in the organism. The extent to which the methyl groups are removed from such a compound and the position of the methyl group first attacked depends upon the kind of animal used. It would seem, *a priori*, that if xanthin is formed by complete removal of methyl groups, this would give some uric acid on further oxidation. Direct experiments indicate that if there is an increase in the excretion of uric acid after administration of methylpurins, it is insignificant in amount.

URIC ACID FROM PROTEID

As we have seen, the early physiologists considered uric acid an antecedent of urea in the destructive metabolism of proteid.

[1] Haig. Uric Acid as a Factor in Causation of Diseases. London (1896).

[2] A. Taylor. The Influence of Various Diets upon the Elimination of Uric Acid and the Purin Bases. Amer. Journ. of Med. Sciences, 118, 141 (1899).

[3] Hess und Schmoll. Ueber die Beziehung der Eiweiss- und Paranukleinsubstanzen der Nahrung zur Alloxurkörper im Harn. Arch. für exp. Path. u. Pharmak., 37, 243 (1896).

[4] Leven. Action physiologique et medicamenteuse de la caféine. Arch. de physiol. norm. et path., t. 1, p. 179 (1868).

[5] G. Zagari e D. Pace. La genesi dell' acido urico e la gotta in riguardo alla patogenesi e all' indirizzo terapeutico. Napoli (1897).

[6] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. 1. Mitteilung. Pflüger's Archiv, 80, 241 (1900).

Thus, in Neubauer's article,[1] and in the old textbooks of Liebig,[2] Lehmann,[3] and Gorup-Besanez,[4] we find the presence of uric acid in the urine attributed to an incomplete oxidation of proteid. This view was based on the ease with which uric acid can be oxidized to urea outside the body, and on the fact that Wöhler and Frerichs [5] found on administration of uric acid to rabbits that there was no increased excretion of uric acid, but a very greatly increased excretion of urea. It may be of interest to state that so recently as 1901 Halliburton [6] states that a diminution of oxidation processes, such as occurs in persons with sedentary habits, is one of the two conditions which lead to an increased excretion of uric acid.

An increased excretion of uric acid was looked upon as an indication of diminished oxidation in the organism. Virchow [7] found that in leukemia there is an increased excretion of uric acid. He believed that this might be due to an oxidation of the hypoxanthin present in the blood through the increased activity of the spleen in this disease, or it might be due to a diminished oxidation power of the organism. He had previously stated [8] that in leukemia there is probably a condition of diminished oxidation brought about by the decreased number of red blood corpuscles. This would occasion, according to him, a diminished internal respiration, — a decreased supply of oxygen to the tissues. In this case there would not be sufficient oxygen present to oxidize the proteid completely to urea, and a larger amount than normally would reach the stage only of uric acid.

As we have already seen, a considerable number of experimenters during the next three decades found the excretion of uric acid in leukemia high. Some of them thought this was due to the oxidation of hypoxanthin from the spleen. We have seen how this idea finally led up to the present views concerning

[1] C. Neubauer. Ueber der Zersetzung der Harnsäure im Tierkörper. Liebig's Ann. der Chem. u. Pharm., 99, 206 (1856).

[2] J. Liebig. Animal Chemistry, or Organic Chemistry in its Application to Physiology and Pathology. Transl. by W. Gregory. (1843) Ed. by J. Webster, Cambridge.

[3] C. Lehmann. Physiologische Chemie, Vol. 1, 2d ed. (1853).

[4] Gorup-Besanez. Lehrbuch der physiol. Chemie, 3. Aufl., 1874.

[5] F. Wöhler und F. Frerichs. Ueber der Veranderungen, welche namentlich organische Stoffe beim Uebergang in den Harn erleiden. Liebig's Ann. der Chem. u. Pharm., 65, 335 (1848).

[6] Halliburton. The Essentials of Chemical Physiology. London (1901).

[7] R. Virchow. Zur pathologischen Physiologie des Blutes. Virchow's Archiv, 5, 43 (1853).

[8] *Ibid.* Virchow's Archiv, 1, 547 (1847).

the source of uric acid. Until Kossel's work on the nucleins, however, about thirty years ago, hypoxanthin was looked upon as a decomposition product of proteid, so that in any case the ultimate physiological source of uric acid was supposed to be proteid.

Liebig seems to have been fully convinced that uric acid is a partial oxidation product of proteid. He stated[1] that if people dwelling in cities who suffer from uric acid concretions go to the country, where they breathe more oxygen, they often get concretions of oxalic acid, an oxidation product of uric acid. If they exercise, and thus breathe still more oxygen, the uric acid is oxidized completely to urea and CO_2. In the urine of animals which drink much water there is, according to Liebig, less uric acid than in other animals; water keeps the sparingly soluble uric acid in solution, and it is therefore more completely oxidized to urea.

Bartels [2] tried to show that an increased excretion of uric acid is due to a disturbance of the relation between the need and the supply of oxygen, that there is always in such a case a relative insufficiency in the amount of oxygen supplied to the tissues. Lehmann [3] had observed an increased excretion of uric acid in fevers. Bartels, however, maintained that this only occurred when with the fever there was also a relatively insufficient oxygen supply. Bartels found the excretion of uric acid increased in chlorosis and leukemia, and attributed it to diminished internal respiration due to lack of red blood corpuscles. Meyer [4] had found that in carbon monoxide poisoning the CO combines with the red blood corpuscles to form a compound so stable that the CO is not replaced by oxygen, and therefore the red blood corpuscles do not take up oxygen. Bartels found increased excretion of uric acid in cases of carbon monoxide poisoning, in which he has been confirmed by Munzer and Palmer.[5] This again seemed to confirm his theory. Jacubasch,[6] who likewise found increased uric acid excretion in leukemia, attributed it to insuffi-

[1] J. Liebig. Animal Chemistry, or Organic Chemistry in its Application to Physiology and Pathology. Transl. of W. Gregory. Ed. by J. Webster, Cambridge (1843).

[2] Bartels. Untersuchungen über die Ursache einer gesteigerten Ausscheidung der Harnsäure in Krankheiten. Deutsche Arch. für klin. Medizin, 1, 13 (1866).

[3] Lehmann. Handbuch der physiol. Chemie, 1, 218 (1853).

[4] L. Meyer. Die Gase des Blutes. Zeitschr. für rationnelle Med. Neue Folge, 8, 256 (1857).

[5] E. Munzer und P. Palmer. Ueber den Stoffwechsel des Menschen bei Kohlendunst- und Nitrobenzolvergiftung. Zeitschr. für Heilkunde, 15, 1 (1894).

[6] H. Jacubasch. Beiträge zur Harnanalyse bei lienaler Leukämie. Virchow's Archiv, 43, 196 (1868).

cient oxidation. Mosler did not find the uric acid excreted always increased in leukemia,[1] and came to the conclusion that this increased excretion occurred only when with the leukemia there was at the same time a relatively insufficient supply of oxygen to the tissues.[2]

A further apparent confirmation of Bartels' theory was seen in the work of Kollmann,[3] Eckhardt,[4] and Sticker.[5] These authors found that the high uric acid in leukemia and emphysema, which was explained as due respectively to deficient internal and external respiration, could be decreased by oxygen inhalation. The work of J. Ranke[6] and others who found the uric acid in the urine, like the urea, dependent on the proteid of the diet, was considered another confirmation of the theory that uric acid comes from proteid.

The work of Nencki and Sieber[7] was also an apparent confirmation of the view that in leukemia there is a condition of diminished oxidation. These authors proposed to measure the power of oxidation of the organism under different conditions by comparing the different amounts of benzene that could be oxidized to phenol. They found that in leukemia less phenol was formed from a definite amount of benzene than normally. It is of interest that they did not find a condition of decreased oxidation by their method in chlorosis and anemia. Kraus and Chwostek[8] by this same method could not observe a condition of decreased oxidation in leukemia. The method of Nencki and Sieber has been shown to be useless.

We have spoken before of the theory of Mares,[9] that the uric

[1] F. Mosler und W. Korner. Zur Blut- und Harnanalyse bei Leukämie. Virchow's Archiv, 25, 142 (1862).

[2] F. Mosler. Zur Diagnose der lienalen Leukämie und der chemischen Beschaffenheit der Transudate und Sekrete. Virchow's Archiv, 37, 43 (1866).

[3] Kollmann. Münchener ärtzl. Intelligenzblatt, 17, No. 22 (1869).

[4] Eckhardt. Die acute Gicht und ihre Behandlung. (Cited by Sticker. Zeitschr. für klin. Medizin, 14, 80 [1888]).

[5] G. Sticker. Beiträge zur Pathologie und Therapie der Leukämie. Zeitschr. für klin. Medizin, 14, 80 (1888).

[6] J. Ranke. Kohlenstoff- und Stickstoff-Ausscheidung des ruhenden Menschen. Arch. f. Anat. u. Physiol., 311 (1862).

[7] M. Nencki und N. Sieber. Ueber eine neue Methode, die physiologische Oxydation zu messen und über den Einfluss der Gifte und Krankheiten auf dieselbe. Pflüger's Archiv, 31, 319 (1883).

[8] F. Kraus und F. Chwostek. Ueber den Einfluss von Krankheiten auf den respiratorischen Gaswechsel und über die Sauerstofftherapie. Wiener klin. Wochenschrift, 4, 605 (1891).

[9] Mares. Sur l'origine de l'acide urique chez l'homme. Archives slaves de Biologie, 3, 207 (1888), and Centralblatt für Med. Wissensch., 26, 2 (1888).

acid owes its formation to the activity of the body cells, especially the cells of the digestive glands. Mares, therefore, considered proteid as the source of uric acid.

Stadthagen [1] attempted to increase the excretion of uric acid by feeding purin bases and nucleins. He obtained negative results and therefore returned to the old idea that uric acid is derived from proteid. The absolute dependence of the amount of uric acid excreted on the proteid of the diet, and its absolute independence of the amount of purin bodies in the food which seemed apparent to him, he considered proof of his view. He also called attention to the fact that starving persons who eat no purin bodies still excrete uric acid, and that suckling children, who receive no purin bodies as food, excrete relatively large amounts of uric acid. The true explanation of the facts cited by Stadthagen as proof of his theory is now apparent, as we have already seen.

The theory that the presence of uric acid in the urine is due to incomplete oxidation had opponents even before the true source of uric acid was known. Thus Panum[2] found that after bleeding dogs, although they had thereby suffered a considerable loss of red blood corpuscles, the internal respiration was unchanged; there was no change in the amount of oxygen taken in and the amount of carbon dioxide formed. It was not possible, apparently, to affect the oxidizing power of the organism.

Voit[3] found that neither by section of the vagus, formation of a pneumothorax, or bleeding, whereby the respiration was disturbed, could he decrease the amount of oxygen taken in or the carbon dioxide given out. Senator [4] bound tightly the thorax of a number of dogs, cats, and rabbits in an attempt to decrease the external respiration. He found, however, that, except in the cases of two of the dogs, there was no increased excretion of uric acid. Even in leukemia, Pettenkofer and Voit,[5]

[1] M. Stadthagen. Ueber das Vorkommen der Harnsäure in verscheidenen tierischen Organen, ihr Verhalten bei der Leukämie und die Frage ihrer Entstehung aus den Stickstoffbasen. Virchow's Archiv, 109, 390 (1887).

[2] P. Panum. Experimentelle Untersuchungen über die Transfusion, Transplantation, oder Substitution des Blutes in theoretischer und practischer Beziehung. Virchow's Archiv, 27, 433 (1863).

[3] C. Voit. Ueber das Gaswechsel nach Durchschneidung der nervi vagi. Sitzungsber. d. königl. bayerischen Akad. de Wissenschaft, 2, 104 (1868).

[4] H. Senator. Experimentelle Untersuchungen über den Einfluss von Respirationsstörungen auf den Stoffwechsel. Virchow's Archiv. 42, 1 (1868).

[5] M. v. Pettenkofer und C. Voit. Ueber den Stoffverbrauch bei einem leukämischen Manne. Zeitschr. für Biol., 5, 319 (1869).

Kraus and Chwostek,[1] and Bohland [2] found that the respiration is not affected. The amount of oxygen taken in and the amount of carbon dioxide expelled were the same as in health on the same food. Naunyn and Reiss [3] found that loss of blood does not influence the amount of uric acid excreted.

The theory that urea has passed through the stage of uric acid in its formation out of proteid never had any proof. It was a mere hypothesis. On the other hand, we have already seen that the quality and quantity of the proteid of the food has no influence on the amount of uric acid excreted. The influence of the food is due solely to the purin bases in it. These bodies oxidize to uric acid. Furthermore, neither uric acid nor the purin bases have ever been obtained as decomposition or oxidation products of proteid. Since, too, as we have seen, uric acid injected into the circulation is excreted in large part unchanged, it is probable that if it were formed as an intermediate product in the destructive metabolism of proteid, it would be excreted in larger quantities.

THE QUESTION OF THE SYNTHESIS OF URIC ACID IN THE BODY

From Glycocoll and Urea

The "fruit cures" have often been recommended in gout. Thus, cherries had been thought by Wöhler and strawberries and grapes by Linne[4] to give clinically good results in gout. Citron has also been highly recommended. Weiss [5] confirmed the clinical results of the older writers and found that the uric acid in the urine is decreased and the hippuric acid increased by a diet containing a large amount of fruit. He found on investigation that quinic acid (hexahydrotetroxybenzoic acid) is the active agent which brings about these results. In a later article he explained how the quinic acid acts.[6] Wöhler had shown that

[1] F. Kraus und F. Chwostek. Ueber den Einfluss von Krankheiten auf den respiratorischen Gaswechsel und über die Sauerstofftherapie. Wiener klin. Wochenschrift, 4, 605 (1891).

[2] K. Bohland. Ueber den respiratorischen Gaswechsel bei verscheidenen Formen der Anämie. Berl. klin. Wochenschrift, 30 417 (1893).

[3] B. Naunyn und L. Reiss. Ueber Harnsäureausscheidung. Du Bois Archiv, für Anat. und Physiol., 381 (1869).

[4] Ebstein. Das Reginnen bei der Gicht. Wiesbaden (1885), p. 49.

[5] J. Weiss. Beiträge zur Erforschung der Bedingungen der Harnsäurebildung. Zeitschr. für physiol. Chem., 25, 393 (1898).

[6] *Ibid.* Eine neue Methode der Behandlung der Harnsäure Diathese. Berl. klin. Wochenschrift, 36, 297 (1899).

hippuric acid is synthesized in the body from glycocoll and benzoic acid. It had been shown also that quinic acid reduces to benzoic acid and then forms hippuric acid with glycocoll. According to Weiss, uric acid is formed by synthesis from glycocoll and urea, and quinic acid, after oxidation to benzoic acid, decreases the amount of uric acid formed by using up the glycocoll formed as intermediate product to form hippuric acid.

Wöhler[1] had previously noted an opposition, so to speak, between uric acid and hippuric acid. In the urine of suckling calves he found uric acid but no hippuric acid. When the milk diet was replaced by a purely vegetable diet, uric acid disappeared, and hippuric acid appeared. These observations of Wöhler were contradicted by Horbaczewski[2] and Weiss.[3] Maly[4] had previously expressed the view that uric acid may be formed in the body by synthesis from glycocoll, and that administration of benzoic acid ought tc use up the glycocoll necessary for the synthesis. He found experimentally, however, that benzoic acid does not decrease the excretion of uric acid.

The views of Weiss seemed very plausible. Strecker[5] had shown that "extra corpus" uric acid can be decomposed into glycocoll carbon dioxide and ammonia, and Horbaczewski[6] had shown that uric acid can be synthesized in the laboratory from glycocoll and urea. Direct attempts to synthesize uric acid in the body by administration of glycocoll and urea gave negative results.[7] On the other hand, we have known since Wöhler's[8] experiment in 1824 that benzoic acid unites with glycocoll in the organism to form hippuric acid. Lautemann[9] showed that quinic acid reduces to benzoic acid outside the body, and also, as we might expect, that quinic acid changes to hippuric acid

[1] Wöhler. Nachr. d. k. Ges. d. Wissensch., zu Göttingen (1849), 5, p. 61.

[2] J. Horbaczewski. Beiträge zur Kenntniss der Bildung der Harnsäure. Wien (1891).

[3] J. Weiss. Beiträge zur Erforschung der Bedingungen der Harnsäurebildung. Zeitschr. für physiol. Chem., 25, 393 (1898).

[4] R. Maly. Ueber das Verhalten der Oxybenzoësäure und Paraoxybenzoësäure in der Blutbahn. Sitzungsber. der Wiener Akad. d. Wissensch., 65, 2. Abt., 39 (1872).

[5] A. Strecker. Bildung von Glycocoll aus Harnsäure. Ann. der Chem. u. Pharm., 146, 142 (1868).

[6] J. Horbaczewski. Synthese der Harnsäure. Monatshefte für Chemie, 3, 796 (1882).

[7] *Ibid.* Weitere synthetische Versuche über die Konstitution der Harnsäure und Bemerkungen über die Entstehung derselben im Tierkörper. Monatshefte für Chemie, 8, 584 (1887).

[8] Berzelius Lehrb. d. Chem. German translation of Wöhler, Vol. 4, Dresden (1831).

[9] E. Lautemann. Ueber die Reduktion der Chinasäure zu Benzoësäure und die Verwandlung derselben in Hippursäure im thierischen Organismus. Ann. der Chem. u. Pharm., CXXV, 9 (1863).

when introduced into the organism. Mattschersky,[1] Meissner and Shepard,[2] and Lewin [3] also found that quinic acid changes to hippuric acid in the organism. Lücke [4] found that berries and vegetables give an increased excretion of hippuric acid, and Loewi [5] found that it is the quinic acid in hay from which the large amount of hippuric acid in the urine of horses and cows is derived. It is very certain, then, that quinic acid changes to benzoic acid in the animal organism and unites with glycocoll to form hippuric acid, and it seemed very possible that glycocoll unites with urea to form uric acid.

Lewin [3] confirmed Weiss's view that quinic acid decreases the excretion of uric acid. Weiss [6] performed one experiment of three days' duration in which he thought he found that the increased excretion of uric acid after thymus feeding was prevented by quinic acid. The results of that experiment, however, do not warrant his conclusion. The quinic acid had practically no effect.

Richter [7] found that the uric acid concretions produced in birds by potassium chromate injections are not so bad when quinic acid in the form of its piperazin salt is given. But Richter's experiments were performed on birds, and in birds the nitrogenous metabolism differs from that of mammals. Further, according to the experiments of Ortowski,[8] Meisls,[9] and Biesenthal,[10] piperazin itself prevents the formation of these concretions.

As a result of the work of Weiss, several preparations containing quinic acid, for example, the lithium, piperazin, urea, and urotropin salts, called respectively urosin, sidonal, urol, and

[1] P. Mattschersky. Zur Entstehung der Hippursäure. Virchow's Archiv, 28, 538 (1863).

[2] Meissner und Shepard. Untersuchungen über die Bildung der Hippursäure. Hanover (1866).

[3] C. Lewin. Beiträge zum Hippursäurestoffwechsel des Menschen. Zeitschr. für klin. Medizin, 42, 371 (1901).

[4] A. Lücke. Ueber die Anwesenheit der Hippursäure im menschlichen Harn und ihre Auffindung. Virchow's Archiv, 19, 196 (1860).

[5] O. Loewi. Ueber die Quelle der Hippursäure im Harn der Pflanzenfresser. Journ. für prakt. Chem., 19, 309 (1879).

[6] J. Weiss. Weitere Beiträge zur Erforschung der Bedingungen der Harnsäurebildung. Zeitschr. für physiol. Chem., 27, 216 (1899).

[7] P. Richter. Ueber die experimentelle Prüfung sogen. "Gichtsmittel" in Allgemeinen und über die Chinasäure und Chinasäure Piperazin im Besonderen. Charitée Annalen, 25, 196 (1900).

[8] W. Ortowski. Vergleichende Untersuchungen über Urotropin, Piperazin, Lysidin, Uricedin, und Natronbicarbonicum bei der harnsäuren Diathese. Zeitschr. für klin. Medizin, 40, 331 (1900).

[9] Meisls. Ungarisches Archiv. für Med., Vol. I., Heft (5–6), (1893).

[10] P. Biesenthal. Wirkung des Piperazins bei kunstlich erzeugten Harnsäureablagerungen im thierischen Organismus. Berl. klin. Wochenschrift, 30, 805 (1893).

chinatropin, also others called ursal, uropherin, uropherinbenzoate, urotropinsalicylate, etc., were recommended and found of clinical value in gout by Weiss,[1] Mylius,[2] Blumenthal,[3] Sternfeld,[4] Salfeld,[5] v. Leyden,[3] Meyer,[3] Ewald,[3] Goldscheider,[3] von Lang,[6] and others. These clinical observations are, of course, not a confirmation of the theory that uric acid can be synthesized from glycocoll and urea, although Weiss[7] has recently tried to defend his theory by using these clinical results as evidence. It is a peculiar fact that all those chemical compounds whose use in gout has been based on scientific observations or pure theory have been found clinically of value by some observers, and even after the scientific observations and theories upon which their use has been based have been proved faulty and erroneous, many good clinicians have still clung to them as possessing some good, though perhaps unexplained, action. This has been true of the inorganic alkaline compounds of sodium, potassium, and lithium, of the organic alkaline bodies of which piperazin and kreatin are examples, of urea, and other bodies, as well as the compounds of quinic acid, and indicates what caution must be used in accepting clinical observations.

Mattschersky,[8] Meissner and Shepard,[9] and Schultzer and Gräbe[10] confirmed Wöhler's work showing that benzoic acid becomes excreted as hippuric acid, and also Lautemann's work showing that quinic acid is excreted as hippuric acid. They also showed that a number of other acids which are derivatives

[1] J. Weiss. Die Chinasäure als Antiarthriticum. Klin.-therap. Wochenschrift, 6, 1544 (1899), *also*

Die Erfolge der Urosinbehandlung bei harnsäurer Diathese. Verhandl. des 18 Kongr. für innere Med. (1900), 477.

[2] Mylius. Ueber die Einwirkung des Sidonal bei Gicht, 14, 658 (1900).

[3] Blumenthal. Ueber Sidonal, ein neues Gichtmittel. München. med. Wochenschrift, 47, 372 (1900), *and discussion by* v. Leyden, J. Meyer, Ewald, Goldscheider, and Meyer. Blumenthal und Lewin. Therapie der Gegenwart (1900), Heft 4.

[4] H. Sternfeld. Die Chinasäure ein neues Heilmittel gegen Gicht. München. med. Wochenschrift, 48, 260 (1901).

[5] Salfeld. Zur Behandlung der Gicht mit Chinasäure. München. med. Wochenschrift, April (1901).

[6] K. von Lang. Ueber ein neues harnsäurelosendes Mittel, das Urosin. Klin.-therap. Wochenschrift, Wien, 10, 247 (1903).

[7] J. Weiss. Erwiderung auf die Arbeit des Herrn Dr. Hupfer. Zeitschr. für physiol. Chem., 38, 198 (1903).

[8] P. Mattschersky. Zur Entstehung der Hippursäure. Virchow's Archiv, 28, 538 (1863).

[9] Meissner und Shepard. Untersuchungen über die Bildung der Hippursäure. Hanover (1866).

[10] O. Schultzer und C. Gräbe. Ueber das Verhalten der aromatischen Säuren im Organismus. Arch. für Anat. und Physiol. 166 (1867).

of benzoic acid, among them salicylic acid, act like benzoic acid and quinic acid in this respect.

We should expect, then, that benzoic acid and salicylic acid would likewise decrease the excretion of uric acid. Yet neither Maly,[1] Lewandosky,[2] or Schreiber and Waldvogel[3] could observe that benzoic acid, nor Bain[4] that lithium benzoate, has any effect on the excretion of uric acid. Only Ulrici[5] observed a slightly decreased excretion of uric acid after administration of benzoic acid. Salicylic acid, in fact, increases the excretion of uric acid according to Schreiber and Waldvogel,[3] Ulrici,[5] Lewandosky,[2] Kumagawa,[6] Bohland,[7] Haig,[8] Bouchard,[9] Lecorché,[10] Magnus-Levy,[11] Byasson,[12] and Salome.[13]

As direct proof against the views of Weiss, we have the researches of Ulrici,[5] Nicolaier,[14] Nicolaier and Hagenburg,[15] Foerster,[16] Lewandosky,[2] and Hupfer,[17] which show that quinic acid has no influence on the excretion of uric acid. Hupfer found that administration of even 25 grams of quinic acid per day had

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[1] R. Maly. Ueber das Verhalten der Oxybenzoësäure und Paraoxybenzoësäure in der Blutbahn. Sitzungsber. der Wiener Akad. d. Wissensch., 65, 2. Abt. 39 (1872).

[2] M. Lewandosky. Versuche über den Einfluss der Benzoësäure auf die Harnsäurebildung. Zeitschr. für klin. Medizin, 40, 202 (1900).

[3] Schreiber und Waldvogel. Beiträge zur Kenntniss der Harnsäureausscheidung unter physiologischen und pathologischen Verhältnissen. Arch. für exp. Path. u. Pharmak., 42, 69 (1899).

[4] W. Bain. The Influence of Some Modern Drugs on Metabolism in Gout. Brit. Med. Journ. (1903), 1, 243.

[5] H. Ulrici. Ueber pharmakologische Beeinflussung der Harnsäureausscheidung. Arch. für exp. Path. u. Pharmak, 46, 321 (1901).

[6] Kumagawa. Ueber die Einwirkung einiger antipyretischen Mittel auf den Eiweissumsatz im Organismus. Virchow's Archiv, 113, 134 (1888).

[7] Bohland. Ueber den Einfluss des salicylsäuren Natrons auf die Bildung und Ausscheidung der Harnsäure. Centralblatt für innere Medizin, 17, 70 (1896).

[8] Haig. Uric Acid in Diseases. 37, London (1896).

[9] Bouchard. Les maladies par ralentissement de la nutrition. 3 ed., 306, Paris (1890).

[10] Lecorché. La goutte, 584, Paris (1884).

[11] A. Magnus-Levy. Ueber Gicht. Zeitschr. für klin. Medizin, 36, 412 (1899).

[12] Byasson. Journ. de Thér., Oct. 10, 1877.

[13] Salome. Ueber den Einfluss des salicylsäuren Natrons auf die Stickstoff und Harnsäureausscheidung beim Menschen. Wiener med. Jahrbücher, 4, 463 (1885).

[14] Nicolaier. Centralbl. für Stoffwechselkrankheiten (1900).

A. Nicolaier. Experimentelles und Klinisches über Urotropin. Zeitschr. für klin. Medizin, 38, 356 (1899).

[15] Nicolaier und Hagenburg. Ueber Chinotropin. Centralbl. f. Stoffwechsel und Verdauungskrankheiten 1, 131 (1900), *also* Maly's Jahresber. über die Fortschritte der Thierchemie, 30, 616 (1900).

[16] Foerster. Versuche über die Beeinflussung der Harnsäureausscheidung mit specieller Berücktsichtigung der Chinasäure und der chinasäuren Salze. Inaug. Dissert, Breslau (1900).

[17] F. Hupfer. Einwirkung von Chinasäure auf Harnsäure und Hippursäureausscheidung. Zeitschr. für physiol. Chem., 37, 302 (1903).

F. Hupfer. Entgegnung an Dr. J. Weiss. Zeitsch. für physiol. Chem., 40, 315 (1903).

no influence on the excretion of uric acid. He found likewise that the addition of large amounts of cherries and grapes had no effect on the excretion of uric acid. His[1] found that citron does not influence the excretion of uric acid. Bain[2] could not find that sidonal has any effect on the excretion of uric acid. Quinic acid does not affect the excretion of uric acid in dogs, according to Taltavall and Gies.[3]

Blumenthal[4] and De la Camp[5] found that quinic acid sometimes decreases the excretion of uric acid and sometimes has no effect. The explanation they gave was that quinic acid decreases the amount of uric acid coming from the purin bodies of the food, but does not influence the amount derived from the body cells. This explains, according to them, the contradictory results of different experimenters. This, however, can scarcely be true, since Hupfer's results show no influence of quinic acid on the uric acid excretion, yet judging from the size of the uric acid excretion, 0.8 to 0.9 gram per day, there must have been purin bodies in the diet. And besides, we know now that the exogenous uric acid comes only from oxidation of purin bodies of the food, and therefore if quinic acid has any influence on this uric acid, Weiss's explanation could not apply.

In a series of experiments carried out over two decades ago,[6] E. and H. Salkowski showed that phenylpropionic acid is formed in intestinal putrefaction of proteid, and that this compound changes to benzoic acid, unites with glycocoll, and is excreted as hippuric acid. Baumann[7] showed that if the intestines be kept

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[1] W. His. Die Ausscheidung von Harnsäure im Urin der Gichtkranken mit besonderer Berücksichtigung der Anfallszeiten und bestimmter Behandlungsmethoden. Deutsche Arch. für klin. Medizin, 65, 156 (1900).

[2] W. Bain. The Influence of Some Modern Drugs on the Metabolism in Gout. Brit. Med. Journ., 1, 243 (1903).

[3] W. Taltavall and W. Gies. The Influence of Chinic Acid on the Elimination of Uric Acid. Proc. Am. Physiol. Soc., Boston (1903), p. xvi; Am. Journ. of Physiol., 9, 16 (1903).

[4] F. Blumenthal. Ueber die Ausscheidung der Harnsäure nach Darreichung von Chinasäure. Charitée Annalen, 25, 34 (1900).

[5] De la Camp. Chinasäure und Gicht. München. med. Wochenschrift, 48, 1203 (1901)

[6] E. Salkowski und H. Salkowski. Ueber die Verdauung von Hydrozimmtsäure bei der Pankreasverdauung. Ber. der Dtsch. chem. Gesell., 12, 107 (1879).

Weitere Beiträge zur Kenntniss der Fäulnissprodukte des Eiweiss. Ber. der. Dtsch. chem. Gesell., 12, 652 (1879).

Ueber das Verhalten der Phenylessigsäure und Phenylpropionsäure im Organismus. Ber. der Dtsch. chem. Gesell., 12, 653 (1899).

Ueber das Verhalten der aus dem Eiweiss durch Fäulniss entstehenden aromatischen Säuren im Thierkörper. Zeitschr. für physiol. Chem., 7, 161 (1882).

[7] E. Baumann. Die aromatischen Verbindungen im Harn und die Darmfäulniss. Zeitschr. für physiol. Chem., 10, 129 (1886).

sterile, no phenylpropionic acid is formed, and no hippuric acid is found in the urine. Weintraud [1] completed this work by showing that the excretion of hippuric acid is parallel with the intestinal putrefaction as expressed by the amount of sulphonic acid in the urine. These experiments indicate that the formation of uric acid and of hippuric acid are entirely independent processes. Since Weintraud [1] found that as much as 24 grams of benzoic acid could be eaten without any appearance of it in the urine, it seems probable that the organism is capable of forming considerable quantities of glycocoll as an intermediate product of metabolism, a quantity many times more than ever appears as uric acid, even if we assume that all the uric acid excreted comes from glycocoll by synthesis.

Weintraud found that the hippuric acid excretion is often, but not always, increased after thymus feeding. He showed, however, that the hippuric acid excretion is parallel with the excretion of sulphonic acid in these cases, and as the latter is an indication of intestinal putrefaction, the increased excretion of hippuric acid is due probably to an increase in the phenylpropionic acid, which also comes from intestinal putrefaction and not from glycocoll.

The theory that quinic acid should decrease the excretion of uric acid is based on the hypothesis that at least a part of the uric acid excreted is formed by synthesis from glycocoll and urea. This hypothesis has no proof. Neither Horbaczewski [2] nor Weiss [3] could observe any increased excretion of uric acid after the administration of glycocoll in the food.

From Lactic Acid and Urea

After Minkowski's [4] experiments on geese with extirpated livers in which he showed that such birds excrete large amounts of ammonium lactate, it seemed that possibly in the mammal organism uric acid might be formed by synthesis from lactic

[1] W. Weintraud. Ueber den Abbau des Nukleins im Stoffwechsel. Verhandl. des 18 Kongr. für innere Med., 232 (1900).

[2] J. Horbaczewski. Weitere synthetische Versuche über die Konstitution der Harnsäure und Bermerkungen über die Entstehung derselben im Tierkörper. Monatshefte für Chemie, 8, 584 (1887).

[3] J. Weiss. Weitere Beiträge zur Erforschung der Bedingungen der Harnsäurebildung. Zeitschr. für physiol. Chem., 27, 216 (1899).

[4] O. Minkowski. Ueber den Einfluss der Leberextirpation auf den Stoffwechsel. Arch. für exp. Path. u. Pharmak., 21, 89 (1886).

acid and urea. This idea was strengthened by the fact that in the following year Horbacszewski[1] succeeded in synthesizing uric acid "extra corpus" from urea and trichlorlactic acid. Direct experiments by Herrmann,[2] Weiss,[3] and Minkowski[4] show, however, that lactic acid taken into the stomach does not increase the excretion of uric acid.

From Glycerin and Urea

Horbaczewski and Kanéra[5] found that glycerin caused increased excretion of uric acid in man, but although the constitutional structure of glycerin is somewhat similar to that of lactic acid, we cannot assume that the increased excretion of uric acid is necessarily due to a synthesis from glycerin and urea, for Munk,[6] Tscherwinsky,[7] and Lewin[8] have shown that the general nitrogenous metabolism also is increased by glycerin. In dogs, Wiener[9] found that glycerin does not give increased excretion of uric acid, and in man Weiss[3] obtained the same result.

From the Monoureides and Urea

Steudel[10] thought that some of the monoureïdes, such as thymin, which is a decomposition product of the nucleoproteids, might, with urea, be synthesized to uric acid. He administered

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[1] J. Horbaczewski. Weitere synthetische Versuche über die Konstitution der Harnsäure und Bemerkungen über die Entstehung derselben im Tierkörper. Monatshefte für Chemie, 8, 584 (1887).

[2] A. Herrmann. Ueber die Abhängigheit der Harnsäureausscheidung von Nahrungs- und Genussmitteln mit Rucksicht auf die Gicht. Deutsche Arch. für klin. Medizin, 43, 273 (1888).

[3] J. Weiss. Beiträge zur Erforschung der Bedingungen der Harnsäurebildung. Zeitschr. für physiol. Chem., 25, 393 (1898).

[4] D. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

[5] Horbaczewski und Kanéra. Ueber den Einfluss von Glycerin, Zucker, und Fett auf die Ausscheidung des Harnsäure beim Menschen. Monatshefte für Chemie, 7, 105 (1886). Sitzungsber. d. kaiserl. Akad. d. Wissensch. zu Wien, 93, 2 abth., 583 (1886).

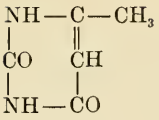
[6] I. Munk. Ob Glycerin ein Nahrungstoff ist. Verhandl. d. physiol. Gesell. zu Berlin (1878). Arch. f. anat. u. physiol., 565 (1878).

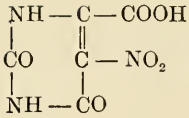
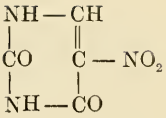
[7] N. Tscherwinsky. Ueber den Einfluss des Glycerins auf die Zersetzung des Eiweisses im Thierkörper. Zeitschr. für Biol., 15, 252 (1879).

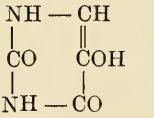
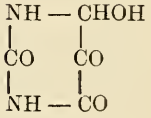
[8] L. Lewin. Ueber den Einfluss des Glycerins auf den Eiweissumsatz. Zeitschr. für Biol., 15, 243 (1879).

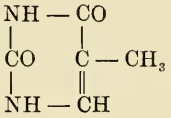
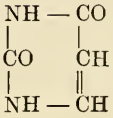
[9] H. Wiener. Ueber synthetische Bildung der Harnsäure im Thierkörper. Beiträge zur chemisch. Physiol. und Pathol., 2, 42 (1902).

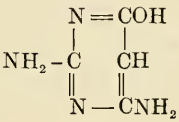
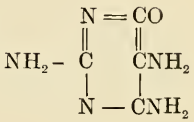
[10] H. Steudel. Das Verhalten einiger Pyrimidinderivate im Organismus. Zeitschr. für physiol. Chem., 32, 285 (1901).

methyluracil 

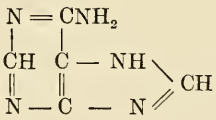
nitrouracilic acid,  nitrouracil, 

isobarbituric acid,  isodialuric acid, 

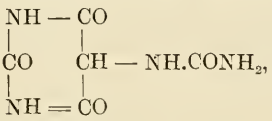
thymin,  2-6-dioxypyrimidin, 

and di- and tri-amino-oxypyrimidin,  and 

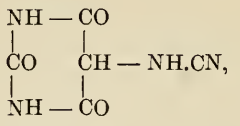
to dogs, but observed no increase in the excretion of uric acid. It is interesting to note that di- and tri-amino-oxy-pyrimidin, the amino derivatives of a monoureide, like adenin,

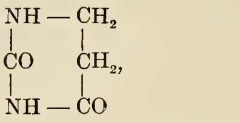


the amino- oxy- di-ureide, proved toxic to dogs and rats and gave crystalline concretions in the kidneys.

In a later series of experiments,[1] Steudel found that feeding of pseudouric acid, 

[1] H. Steudel. Futterungsversuche in der Pyrimidingruppe. Zeitschr. für physiol. Chem., 39, 136 (1903).

isouric acid, 

or hydrouracil,  did not lead to an increased excretion of uric acid in dogs. Pseudouric acid easily changes to uric acid on fusion with oxalic acid.[1] Isouric acid changes to uric acid on boiling with HCl.[2] The fact that Steudel's experiments were performed upon dogs indicates that they are of doubtful value as conclusive results.

Minkowski[3] attempted to obtain an increased excretion of uric acid in dogs by administration of urea and allantoin, but failed.

From Other Compounds

Hopkins and Hope[4] noticed that the increased excretion of uric acid after eating meat comes more quickly than the increase in the excretion of urea. Since nuclein is absorbed only in the intestines, he thought the increased excretion could not be due to nucleins. These authors found likewise that the extract of thymus gland freed from nuclein by digestion with pepsin hydrochloric acid gave increased excretion of uric acid. They thought, therefore, that a formation of uric acid in some other way than by oxidation of purin bodies, probably by synthesis, was indicated. Smith-Jerome[5] found that the thymus extract of Hopkins and Hope contained free purin bases, partly present originally and partly formed by the digestion of the thymus. This would account for the increased excretion of uric acid.

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[1] A. Schlieper und A. Baeyer. Untersuchungen über die Harnsäuregruppe. Liebig's Ann. der Chem. u. Pharm., 127, 3 (1863).

[2] Mulder. Ueber die Synthese von Harnsäure und über Isoharnsäure. Ber. der Dtsch. chem. Gesell., 6, 1235 (1873).

[3] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

[4] F. Hopkins and W. Hope. On the Relation of Uric Acid Excretion to Diet. Journ. of Physiol., 23, 271 (1898).

[5] W. Smith-Jerome. Further Proofs of the Origin of Uric Acid from Nuclein Compounds and Drivatives. Journ. of Physiol., 25, 98 (1899).

The only direct indication that we have of a possible formation of uric acid by synthesis in mammals is the work of Wiener. This author found [1] that uric acid is formed in the autodigestion of cut-up ox liver. If the alcohol extract of another liver be added, more uric acid is formed in a definite length of time. Since the alcoholic extract does not contain purin bodies, Wiener believed that he had an indication that there was something in the alcoholic extract from which uric acid was formed by a synthetic process. It seems possible to us, however, that the uric acid may be formed from the nucleoproteids of the cell nuclei by the oxidizing action of something in the liver. The alcoholic extract of another liver may contain something which simply hastens the oxidation process. In the dog liver there is no uric acid found on autodigestion, possibly because it is further oxidized to allantoin.

It will be remembered that Salkowski [2] long ago showed that if weighed amounts of purin bases be added to cut-up spleens or livers, and the mixture digested with blood and air, an oxidation of the bases to uric acid takes place. If the spleen or liver be left out in the experiment, the oxidation does not take place. There is something in the spleen and liver necessary to carry on the process.

The action of spleen, liver, and other organs in the transformation of purin bases to uric acid has been much studied recently. It will be remembered that in the study of the occurrence of purin bases in the tissues, we saw that different purin bases were obtained in fresh organs from those obtained in organs which had undergone self-digestion. The results of Levene,[3] who studied this subject, show that the amino purins change to the oxypurins in the process of autolysis. According to Jones,[4] there is an enzyme in thymus which can decompose the nucleoproteid and give the free amino purins, and another enzyme which changes the amino purins to the oxypurins. In pancreas there is an

[1] H. Wiener. Ueber Zersetzung und Neubildung der Harnsäure im Tierkörper. Verhandl. des 18t Kongr. für innere Med., 622 (1899), and Arch. für exp. Path. u. Pharmak., 42, 375 (1899).

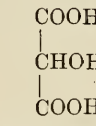
[2] E. Salkowski. Ueber Autodigestion der Organe. Zeitschr. für klin. Medizin, 17. Suppl. 77 (1890).

[3] P. Levene. The Autolysis of Animal Organs. II. Hydrolysis of Fresh and Self-digested Glands. Am. Journ. of Physiol., 12, 276 (1904).

[4] W. Jones. Uber das Enzyme der Thymusdrüse. Zeitschr. für physiol. Chem., 41, 101 (1904).

enzyme which changes the guanin to xanthin.[1] In the spleen there is an enzyme which changes adenin to hypoxanthin.[2] According to Jones "guanase," the ferment which changes guanin to xanthin, is a different body from "adenase," which changes adenin to hypoxanthin, for in the liver the adenin changes to hypoxanthin, but the guanin does not change to xanthin.[2] Schenk[3] agrees with Jones that the guanase and adenase are different ferments, but he differed from Jones in finding an adenase but not guanase in pancreas. The view of Schittenhelm[4] seems more probable. According to this author, there is one ferment which splits the purin bases from nucleic acid; another which changes the amino purins to the oxypurins, and a third which oxidizes hypoxanthin and xanthin to uric acid. These ferments are widely distributed in the various organs, liver, spleen, lungs, and muscle. Schittenhelm[4] isolated both the oxidase and the ferment which splits off the amino group to some extent. These ferments do not act on the nucleic acid. This author believes that the ferment which changes the amino purins to the oxypurins is the "desamidierende" enzyme which Lang[5] has found widely distributed in the organism. Burian[6] likewise has found in organs an enzyme which oxidizes oxypurins to uric acid.

By the addition of tartronic acid,



[1] W. Jones und C. Partridge. Uber die Guanase. Zeitschr. für physiol. Chem., 42, 343 (1904).

[2] W. Jones und M. Winternitz. Uber die Adenase. Zeitschr. für physiol. Chem., 44, 1 (1905).

[3] M. Schenk. Die bei der Selbstverdauung des Pankreas auftretenden Nukleïnbasen. Zeitschr. für physiol. Chem., 43, 406 (1905).

[4] A. Schittenhelm. Ueber die Harnsäurebildung in Gewebsauszügen. Zeitschr. für physiol. Chem., 42, 251 (1904).

Ueber die Fermente des Nukleïnstoffwechsels. Zeitschr. für physiol. Chem., 43, 228 (1904).

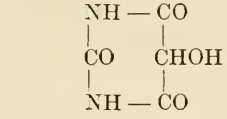
[5] S. Lang. Ueber Desamidierung im Tierkörper. Hofmeister's Beiträge, 5, 321 (1904).

[6] R. Burian. Die Bildung der Harnsäure im Organismus des Menschen. Med. Klinik, 1, 131 (1905).

Ueber die Oxydative und die vermeintliche synthetische Bildung von Harnsäure in Rinderleberauzug. Zeitschr. für physiol. Chem., 43, 497 (1905).

Die Herkunft der endogenen Harnpurine bei Mensch und Säugethiere. Zeitschr. für physiol. Chem., 43, 532 (1905).

or its monoureïde, dialurie acid,



to a quantity of cut-up ox liver, and subjecting the mass to autodigestion for four hours, in Wiener's experiments, a slightly larger quantity of uric acid was formed than when the tartronic acid or dialuric acid were left out. The addition of other similar bodies, such as malonic acid, barbituric acid, and glycerin, had no effect.

Wiener supposed that uric acid was synthesized from the tartronic acid and the dialuric acid, but Burian[1] has explained Wiener's results in another way, namely, that these bodies merely increase the rate at which the purin bases in the organ are changed to uric acid. Burian found that if the liver is first freed in large part from the purin bodies, and then allowed to undergo self-digestion, no uric acid is formed, even when tartronic acid or dialuric acid is added. When xanthin was added to the liver, uric acid was formed, and the rate of oxidation of xanthin to uric acid was increased, when dialuric acid or tartronic acid was added. Salicylic acid likewise hastened the reaction. Wiener[2] found that the administration per os of exceedingly large quantities (10 grams to 15 grams) of dialuric acid, malonic acid, and lactic acid gave an exceedingly slight increase in the excretion of uric acid in man. The increased excretion is so slight as to seem but a doubtful confirmation of Wiener's views.

We have already seen that we can vary the food in calories, proteid, fats, and carbohydrates without affecting the excretion of uric acid, provided the amount of purin bodies in the food is not varied. Fats do not increase the excretion of uric acid, according to the experiments of Horbaczewski and Kanéra,[3]

[1] R. Burian. Die Bildung der Harnsäure im Organismus des Menschen. Med. Klinik, 1, 131 (1905).

Ibid. Ueber die oxydative und die vermeintliche synthetische Bildung von Harnsäure in Rinderleberauszug. Zeitschr. für physiol. Chem., 43, 497 (1905).

[2] H. Wiener. Ueber Zersetzung und Neubildung der Harnsäure im Tierkörper. Verhandl. des 18t Kongr. für innere Med., 622 (1899), *and* Arch. für exp. Path. u. Pharmak., 42, 375 (1899).

[3] Horbaczewski und Kanéra. Ueber den Einfluss von Glycerin, Zucker. und Fett auf die Ausscheidung der Harnsäure beim Menschen. Sitzungsber. d. kaiserl. Akad. d. Wissensch. zu Wien., 93, 2 Abth., 583 (1886), and Monatshefte für Chemie, 7, 105 (1886).

Herrmann,[1] Kaufmann and Mohr,[2] and Laquer.[3] The experiments of Horbaczewski and Kanéra,[4] Weiss,[5] and Kaufmann and Mohr [2] show that carbohydrates likewise have no effect.

Only Meissner [6] and Rosenfeld and Orgler [7] find that carbohydrates or fats increase the excretion of uric acid, and their work is open to criticism.

Meissner used dogs in his experiments and used an inaccurate method for determining uric acid. It is on the work of Meissner that the idea is based of forbidding the use of fats in the uric acid diathesis. It may be noted that in accord with the old view that uric acid is a product of incomplete oxidation, Meissner stated that the body has only a certain amount of oxygen at its disposal, and that if large quantities of fats are administered, the supply of oxygen will be largely used by them, and there will be insufficient oxygen to oxidize the uric acid to urea.

Rosenfeld and Orgler [7] found a greater excretion of uric acid on a diet containing 600 grams of meat than on one containing 800 grams meat, a fact which indicates that their work is of doubtful value. Again, in an experiment lasting four days, during which time 600 grams meat per day was taken, 1.005 grams uric acid was excreted the first day, .772 gram the second, .576 gram the third, and .934 gram the fourth. Either the food on these days contained varying amounts of purin bodies, the analyses are incorrect, or the patient was not in a normal healthy condition. The daily variation of excretion is far too great for a fixed diet. On two following days, 150 grams of

[1] A. Herrmann. Ueber die Abhangigheit der Harnsäureausscheidung von Nahrungs und Genussmitteln mit Rücksicht auf die Gicht. Dtsch. Arch. für klin. Med., 43, 273 (1888).

[2] M. Kaufmann und L. Mohr. Beiträge zur Alloxurkörperfrage und zur Pathologie der Gicht. Dtsch. Arch. für klin. Med., 74, 141 (1902).

[3] B. Laquer. Ueber die Beeinflussung der Alloxurkörper (Harnsäure + Xanthinbasen)- Ausscheidung durch Milchdiät und über Fettmilch bei Gicht. Berl. klin. Wochenschrift, 32, 807 (1896).

[4] Horbaczewski und Kanéra. Ueber den Einfluss von Glycerin, Zucker und Fett auf die Ausscheidung der Harnsäure beim Menschen. Sitzungsber. d. kaiserl. Akad. d. Wissensch. zu Wien., 93, 2 Abth., 583 (1886), and Monatshefte für Chemie, 7, 105 (1886).

[5] J. Weiss. Weitere Beiträge zur Erforschung der Bedingungen der Harnsäurebildung. Zeitschr. für physiol. Chem., 25, 393 (1898).

[6] G. Meissner. Ueber das Entstehen der Bernsteinsäure im thierischen Stoffwechsel. Zeitschr. für rationelle Med., 24, 97, 1865.

[7] G. Rosenfeld und Orgler. Zur Behandlung der harnsäuren Diathese. Centralblatt für innere Medizin, 17, 42 (1896).

G. Rosenfeld. Grundzuge der Berhandlung der harnsäuren Diathese. Verhandl. des 14t Kongr. für innere Med., 321 (1896).

Harnsäure und Diäte. Allgem. medicinische Centralzeitung, 65, 789 (1896).

butter were added to the diet, and 1.003 grams uric acid was excreted on one day and .785 gram on the next. On two consecutive days, during which the diet consisted of 800 grams meat and 150 grams butter, the excretion of uric acid was, respectively, 1.202 grams and .694 gram. In these experiments again the variations in the amounts of uric acid excreted, when the diet was fixed, are greater than can be accounted for on the assumption that the patient is normal and the purin content of the food constant.

From Burian and Schur[1] we get evidence which seems to indicate pretty clearly that if uric acid can be formed synthetically in mammals, that which is so formed is not, as in birds, affected by the quality or the quantity of the diet. In a series of experiments of their own and of Krüger and Schmidt, Loewi, and Horbaczewski, in which the quality and quantity of the diet was of the most varied character in the different experiments, they compared the amount of uric acid actually excreted with the amount they calculated should be excreted, assuming that all the exogenous uric acid comes from the purin bodies of the food. In their experiments they assumed that 52 per cent of the hypoxanthin of the food is excreted as uric acid. The results obtained by calculation agreed remarkably closely with the results obtained by analysis, showing that if compounds in the food other than the purin bodies can influence the excretion of uric acid, the influence is insignificant.

Siven[2] as a result of his work, came to a conclusion identical with that of Burian and Schur, namely, that the foodstuffs other than purin bodies have no influence on the excretion of uric acid.

To summarize briefly the results we may say that there is no positive experimental evidence at present to show that uric acid can be synthesized in the mammal organism. Since nothing in foodstuffs free from purin bodies has any apparent effect on the excretion of uric acid, we must assume that there is nothing in our food or the decomposition products of our food from which uric acid can be synthesized. We have not yet enough data concerning the formation of uric acid in muscular activity to give an explanation, but it may be possible that this is due to some sort of syn-

[1] R. Burian und H. Schur. Das quantitativen Verhalten der menschlichen Harnpurinausscheidung. Pflüger's Archiv, 94, 273 (1903).

[2] V. Siven. Zur Kenntniss der Harnsäurebildung im menschlichen Organismus unter physiologischen Verhältnissen. Skand. Arch. f. Physiol., 11, 123 (1901).

thetic process, perhaps analogous somewhat to the synthesis of nucleoproteid in the organism.

The Decomposition of Uric Acid in the Body

The old view of the significance of uric acid in metabolism, as we have already seen, was that uric acid is an intermediate product in the oxidation of proteid matter to urea. This view, which is expressed in the textbook of Liebig,[1] was based on the fact that outside the body uric acid is easily oxidized to urea, and, further, on the fact that Frerichs and Wöhler[2] fed uric acid to rabbits and dogs, but did not find it again in the urine. They did find, however, an increased excretion of urea. According to this theory, the presence of uric acid in the urine is due to insufficient oxidation. The more complete the process of oxidation, the less uric acid is found in the urine.

Even after Liebig's theory was shown to be incorrect, and it was found that the metabolism of proteid and the metabolism of uric acid are quite independent, the idea prevailed for a long time that uric acid is destroyed by the animal organism, and that the uric acid found in the urine is but a small part of the uric acid at one time present in the body. In fact, it is only recently that the work has been done which indicates that in man a considerable part of the uric acid formed in the body is excreted unchanged. In different classes of animals the fraction excreted unchanged is different. The products of oxidation of uric acid in different classes of mammals seem to be different, but this cannot yet be considered as definitely settled.

The fact that only a part of the uric acid corresponding to the purin bodies in the food is excreted has been explained in different ways. Garrod and certain others have maintained that an explanation is afforded if we assume that uric acid is formed in the kidneys. According to Kolisch and Dostal,[3] we have a proof of this theory in their experiments. They showed that in kidney diseases the excretion of uric acid is decreased, and the excretion

[1] J. Liebig. Animal Chemistry, or Organic Chemistry in its Application to Physiology and Pathology. Transl. by W. Gregory. Ed. by J. Webster (1843).

[2] F. Frerichs und F. Wöhler. Ueber Veränderungen welche namentlich organische Stoffe bei ihrem Uebergang in der Harn erleiden. Liebig's Ann. der Chem. u. Pharm., 65 335 (1848).

[3] R. Kolisch und H. Dostal. Das Verhalten der Alloxurkörper im pathologischen Harn. Wien klin. Wochenschrift, 8, 435 (1895).

of purin bodies increased. These authors, however, used the inaccurate Krüger-Wulff method for determining the purin bodies in urine. We shall see later that uric acid is not formed in the kidneys.

The explanation offered by Lüthje[1] seems satisfactory. Purin bases and uric acid are bodies which can be excreted. A part of the blood has been freed from purin bodies before reaching the kidneys. The rest of the blood contains a certain amount of purin bodies and these are excreted. Burian and Schur[2] think that their work confirms this view, in dogs at any rate. By increasing the blood supply of the kidneys of dogs through the action of diuretics, without at the same time affecting the blood supply of the liver, which organ, in dogs, as we shall see, destroys uric acid, they increased the excretion of uric acid.

Another point to be considered in a study of the decomposition of uric acid in the body is that sometimes concretions of uric acid may be stored up in certain parts of the body. In such cases the amount of uric acid in the urine cannot be considered a measure of the amount of uric acid formed. It will be seen, however, that normally such a retention of uric acid does not occur. The importance of a consideration of the decomposition of uric acid in the body in general and the retention of uric acid in particular will be seen when we reach the subject of gout.

DECOMPOSITION PRODUCTS OF URIC ACID OUTSIDE THE BODY

By the action of different agents, uric acid undergoes decomposition in a number of different ways. There are three methods of decomposition which give products found in the animal body, and which, therefore, have been considered physiologically important by different authors.

1. By the action of nitric acid, alloxan and urea are formed. On warming, the alloxan decomposes further to parabanic acid, then to oxaluric acid, and finally to oxalic acid. According to Salkowski,[3] oxalic acid and urea are formed directly from uric acid by the action of $FeCl_3$.

2. By the action of potassium permanganate, uric acid de-

[1] H. Lüthje. Der heutige Stand der Alloxurkörperfrage. Arch. für Verdauungskrankheiten, 2, 345 (1896).

[2] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. 2. Mitth. Pflüger's Archiv, 87, 239 (1901).

[3] E. Salkowski. Beiträge zur Chemie des Harns. Pflüger's Archiv, 2, 351 (1869).

composes to allantoin. On further oxidation, the allantoin decomposes to oxalic acid and urea.

3. When uric acid is heated with hydriodic acid in a sealed tube, glycocoll, ammonia, and carbonic acid are formed.

Carbon dioxide, ammonia, urea, glycocoll, allantoin, and oxalic acid are all found in the mammal organism.

IN RABBITS

Early Work

Wöhler and Frerichs[1] performed four experiments on rabbits, in which they fed in each case 2.5 grams potassium urate. They found an increased excretion of urea, and a sediment of calcium oxalate in the urine, but no sediment of uric acid or urates. They assumed that the uric acid had been oxidized to allantoin and then to urea and oxalic acid. Neubauer[2] fed 24 grams uric acid to a rabbit. He found that there occurred an increased excretion of 15.95 grams urea. Theoretically, 17.13 grams urea can be obtained from 24 grams uric acid. Neubauer found a small amount of uric acid in the urine, but no considerable amount of oxalates. When uric acid was administered at night, he found a sediment of oxalates in the urine the next morning. According to Neubauer, the presence of the oxalates is due to the fact that the oxidation processes are retarded at night, and that, therefore, the uric acid is not oxidized completely to carbon dioxide and urea.

At the time of Wöhler and Frerichs and Neubauer, there was no accurate method in use for the quantitative determination of urea. Liebig's method, which was the method used, gives the creatin, uric acid, and other nitrogenous bodies as well as urea. The formation of a sediment of oxalates in the urine, like the formation of a sediment of urates, is determined, not altogether by the amount present, but also by the reaction of the urine, and by the amounts of other bodies present.[3] The observations of Wöhler and Frerichs and Neubauer are, therefore, worthless.

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[1] F. Wöhler und F. Frerichs. Ueber Veränderungen, welche namentlich organisch Stoffe bei ihrem Uebergang in den Harn erfahren. Ann. d. Chem. u. Pharm., 65, 335 (1848).

[2] C. Neubauer. Ueber die Zersetzung der Harnsäure im Tierkörper. Ann. der Chem. u. Pharm., 99, 206 (1856).

[3] *Ibid.* Arch. f. wissensch. Heilk. (1858), 1.

Absorption and Excretion as Uric Acid or Urea

Burian and Schur[1] found that 17.7 per cent of the uric acid injected into a rabbit is excreted unchanged. About the same fraction of the hypoxanthin injected is found as uric acid in the urine.

Croftan[2] performed experiments which showed directly that some of the uric acid fed to rabbits is excreted unchanged. He injected uric acid into rabbits and found from 11 to 17 per cent unchanged in the urine. None was found in the feces, in the blood, or in the internal organs. He concluded that the other 83 to 89 per cent must have been destroyed.

According to Bendix and Schittenhelm,[3] very little of the uric acid taken in the food is excreted unchanged, but when it is given subcutaneously or intravenously, a large part is excreted unchanged.

Salkowski[4] has attempted to determine the amount of uric acid absorbed by rabbits, and its fate in the body. This author determined the total nitrogen, the urea, and the total sulphur, and in one case also the uric acid, in the urine of rabbits fed on a fixed diet. He then added uric acid to the food and found that the excretion of total nitrogen and urea was increased. The excretion of sulphur was not increased. The increased excretion of nitrogen, therefore, was due to an absorption of the uric acid and not to increased decomposition of body proteid, since the ratio N : S in the urine is nearly constant where there is simply a variation in the proteid metabolism. In this way Salkowski found that a variable part of the uric acid, from one half to the whole, is absorbed and excreted, mostly as urea. A small part is excreted as uric acid, and probably, according to Salkowski, a small part as allantoin.

That some uric acid can escape oxidation in rabbits is indicated by the fact that Ebstein and Nikolaier[5] found small crystals of

[1] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. 2. Mitth. Pflüger's Archiv, 87, 239 (1901).

[2] A. Croftan. Synopsis of experiments on the transformation of circulating uric acid in the organism of man and animals. Med. Record, 64, 16 (1903).

[3] E. Bendix und A. Schittenhelm. Ueber die Ausscheidungsgrösse per os, subcutan und intravenös eingeführten Harnsäure beim Kaninchen. Zeitschr. für physiol. Chem., 42, 461 (1904).

[4] E. Salkowski. Ueber das Verhalten in den Magen eingeführter Harnsäure im Organismus. Zeitschr. für physiol. Chem., 35, 495 (1900).

[5] W. Ebstein und A. Nikolaier. Ueber die Ausscheidung der Harnsäure durch die Niere. Virchow's Archiv, 143, 337 (1896).

uric acid in the kidneys after subcutaneous, intravenous, and intraperitoneal injections of uric acid.

Oxidation to Allantoin, Oxalic Acid, Oxaluric Acid, Alloxan, Alloxantin, and Parabanic Acid

Administration of uric acid probably does not increase the excretion of allantoin. Salkowski did not find allantoin in the urine by direct experiment after feeding uric acid to rabbits, nor did Mendel and White,[1] who introduced uric acid and urates intravenously. It is probable that in this animal allantoin is almost completely oxidized.

Luzzato[2] did not find allantoin in the urine of rabbits after feeding allantoin to them. He did find, however, that the oxalic acid in the urine was very largely increased. In an experiment in which about 3 grams allantoin were fed, and about 1.5 grams absorbed, the excretion of oxalic acid was increased by about .0438 gram. According to Hildebrandt,[3] and Autenrieth and Barth,[4] oxalic acid administered per os does not reappear in the urine. On the other hand, Hildebrandt[3] found that about 10 per cent of the sodium oxalate injected subcutaneously appears in the urine. According to this, the .0438 gram of oxalic acid found in the urine in Luzzato's experiment represents about .4380 gram oxalic acid formed in the body. This is about 27 per cent of the weight of the allantoin administered. According to the reaction of Claus[5] for the formation of oxalic acid from allantoin, $3C_4H_6N_4O_3 + 15H_2O = 12NH_3 + 6CO_2 + 2C_2H_2O_4 + C_2H_4O_2 + 2H_2O$, the weight of oxalic acid formed is about 38 per cent of the allantoin decomposed. If, then, allantoin were formed by the oxidation of uric acid in the organism of the rabbit, it is probable that it would be further decomposed in large part to oxalic acid.

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[1] L. Mendel and B. White. On the intermediary metabolism of the purin bodies. The formation of allantoin in the animal body. Am. Journ. of Physiol., 12, 85 (1904).

[2] A. Luzzato. Ueber das Verhalten des Allantoins im Tierkörper. Zeitschr. für physiol. Chem., 38, 537 (1903).

[3] H. Hildebrandt. Ueber eine experimentelle Stoffwechselabnormität. Zeitschr. für physiol. Chem., 35, 141 (1902).

[4] W. Autenrieth und H. Barth. Ueber Vorkommen und Bestimmung der Oxalsäure im Harn. Zeitschr. für physiol. Chem., 35, 327 (1902).

[5] A. Claus. Zur Kenntniss der Harnsäuregruppe. Ber. der Dtsch. chem. Gesell., 7, 226 (1874).

Luzzato[1] found that the administration of uric acid per os does not increase the excretion of oxalic acid. This indicates that the theory of Neubauer and of Wöhler and Frerichs is incorrect. It indicates, also, that uric acid does not oxidize to allantoin in the rabbit, since the allantoin, as we have seen, would be oxidized further to oxalic acid. Luzzato[1] found, too, that oxaluric acid oxidizes to oxalic acid in the rabbit, so that it seems improbable that any oxaluric acid is formed by the oxidation of uric acid. Lusini[2] found that alloxan, alloxantin, and parabanic acid are toxic to rabbits in very small quantities, so that these are probably not formed by the oxidation of uric acid.

Oxidation to Glycocoll

Wiener's work is the most indicative of the way in which uric acid is oxidized in the rabbit.[3] Wiener found that the toxic dose of benzoic acid is 1.7 grams per kilo of rabbit. When 1 gram benzoic acid is administered, it combines with glycocoll and gives about .83 gram of hippuric acid. When more than 1 gram benzoic acid is given, about the same amount of hippuric acid is excreted. The excess of benzoic acid is passed off unchanged. This indicates that the rabbit organism is able to furnish a maximum of about .34 gram glycocoll to combine with benzoic acid to form hippuric acid. When glycocoll is administered with the hippuric acid, this glycocoll combines with some benzoic acid to form hippuric acid. There is then more hippuric acid and less free benzoic acid excreted than without the glycocoll. The fatal dose of benzoic acid is thereby raised from 1.7 grams to 2.39 grams per kilo. The excretion of hippuric acid is increased from .83 gram to 1.48 grams. The administration of uric acid with the benzoic acid has the same effect as the administration of glycocoll. The administration of .36 gram uric acid increased the excretion of hippuric acid from .83 gram to about 1.14 grams per day per kilo of rabbit, and enabled rabbits to stand a dose of 1.7 grams

[1] A. Luzzato. Zur Physiologie der oxalsäure und oxalursäure im Harn. Zeitschr. für physiol. Chem., 37, 225 (1903).

[2] V. Lusini. Ueber die biologische Wirkung der Ureïde mit Beziehung auf ihre chemische Konstitution. 1. Alloxan, Alloxantin, und Parabansäure. Chem. Centralbl., 1, 1074 (1895).

[3] H. Wiener. Ueber das Glycocoll als intermediäres Stoffwechselprodukt. Arch. für exp. Path. u. Pharmak., 40, 313 (1897).

benzoic acid without fatal consequences. This indicates, according to Wiener, that in the rabbit uric acid decomposes with formation of glycocoll. This is the way uric acid decomposes when heated with hydrochloric acid.

Wiener[1] does not believe that the uric acid decomposes first to allantoin or hyantoin and then to glycocoll, for in a later article, he showed that 1.7 grams benzoic acid is still poisonous to a rabbit after administration of hyantoin or allantoin. Neither does he think that uroxanic acid is an intermediate oxidation product between uric acid and glycocoll, since Sundwik showed that uroxanic acid cannot decrease the poisonous action of benzoic acid. Nor does he think that the uric acid decomposes first to alloxan and this later to glycocoll and parabanic acid, for alloxan and parabanic acid are poisonous, according to both Wiener and Lusini.[2]

Burian and Schur[3] state that it is possible that the uric acid administered to rabbits may increase the formation of glycocoll without necessarily changing into glycocoll. Cohn[4] and Wiener[5] have since indulged in a polemic over the whole question of the glycocoll formation in the body without being able to come to an agreement.

Wiener performed but three experiments in uric acid feeding. In these experiments the average increase in the excretion of hippuric acid after uric acid feeding was more than could be accounted for by assuming that the uric acid was quantitatively changed to glycocoll according to the reaction. This may be due to experimental errors, but, at any rate, Wiener's work needs confirmation in some way before we can accept his conclusions as definitely proved.

Summary

To sum up, then, it seems probable that in the rabbit uric acid is absorbed in variable quantities when administered per os.

[1] H. Wiener. Ueber Zersetzung und Neubildung der Harnsäure im Thierkörper. Arch. für exp. Path. u. Pharmak., 42, 375 (1899), and Verhandl. des 17t Kongr. für innere Med., 622 (1899).

[2] V. Lusini. Ueber die biologische Wirkung des Ureïde mit Beziehung auf ihre chemische Konstitution. 1. Alloxan, Alloxantin, und Parabansäure. Chem. Centralbl., 1, 1074 (1895).

[3] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. 2. Mitth. Pflüger's Archiv, 87, 239 (1901).

[4] R. Cohn. Zur Frage des Glykokolvorraths im thierischen Organismus. Prager mediz. Wochenschrift, 27, 269, und 287 (1902).

[5] H. Wiener. Zur Frage des Glykokolvorraths im thierischen Organismus. Prager mediz. Wochenschrift, 27, 290 (1902).

The amount of the uric acid absorbed which is excreted unchanged is very small according to Salkowski, about 17 per cent according to Burian and Schur, and 11 to 17 per cent according to Crofton. The uric acid decomposes, giving glycocoll according to Wiener, and urea according to Salkowski. It may, of course, be true that the uric acid decomposes first to glycocoll and then to urea, or into both glycocoll and urea. It seems improbable that more than very small amounts of allantoin, alloxan, oxalic acid, parabanic acid, uroxanic acid, or alloxantin are formed either as intermediate, or as end products.

DOGS AND CATS

Early Work

Gallois [1] fed potassium urate to dogs, but did not find that it gave increased excretion of urea. Zabelin [2] fed 44 grams uric acid to two dogs in the course of several weeks and found that it was almost all excreted as urea. These authors, however, determined urea by Liebig's method, — precipitation with nitrate of mercury and determination of nitrogen in the precipitate. This gives the sum of the urea, uric acid, hippuric acid, purin bases, creatin, and other nitrogenous bodies. Zabelin's results are, therefore, worthless, and probably also those of Gallois.

Absorption and Excretion as Uric Acid and Urea

Salkowski [3] found by the same method of experiment that he used in the case of rabbits that a variable part, from 20 to 50 per cent, of the uric acid administered was absorbed. Of this, a part was excreted as urea. That the dog can excrete a considerable quantity of uric acid, either oxidized or unoxidized, is shown by the fact that Ebstein and Nikolaier [4] observed no evil effects on a dog and no concretions of uric acid in the kidneys when 10 grams uric acid per day were fed to it for five and one-half months.

In Zabelin's experiment there was a slight increase in the

[1] Gallois. Experiences sur l'urée et les urates. Comptes rendus, 44, 734 (1857).

[2] Zabelin. Ueber die Umwandlung der Harnsäure im Thierkörper. Ann. d. Chem. u. Pharm., 2 Suppl., 326 (1863).

[3] E. Salkowski. Ueber das Verhalten in den Magen eingefuhrter Harnsäure im Organismus. Zeitschr. für physiol. Chem., 35, 495 (1902).

[4] W. Ebstein und A. Nikolaier. Ueber die Ausscheidung der Harnsäure durch die Niere. Virchow's Archiv, 143, 337 (1896).

excretion of uric acid after feeding uric acid. Meissner[1] also found a slightly increased excretion of uric acid after feeding 1 gram sodium urate to a dog. Salkowski[2] fed 4 grams of uric acid to each of two dogs in two days, but did not observe an increased excretion of uric acid.

Swain[3] found from 2 to 3 per cent of the uric acid administered to dogs excreted unchanged. Burian and Schur[4] found that from 4 to 5 per cent of the uric acid injected into dogs is excreted unchanged. This same fraction of the purin bodies administered is excreted as uric acid whether it be given as uric acid, hypoxanthin, or thymus, and whether it be given per os or injected. In one of the dogs used the fraction excreted was always 12 per cent.

Minkowski[5] also found that about 4 per cent of the hypoxanthin fed is excreted as uric acid. According to Spiegelberg,[6] the full-grown dog destroys all but about 5.6 per cent of the uric acid administered. He found that the puppy destroys less, and that after subcutaneous administration of uric acid to puppies concretions of uric acid are found in the kidneys. Minkowski's experiments,[5] too, in which the administration of nuclein and thymus gave increased excretion of uric acid, show that not all the uric acid formed in the dog is oxidized.

According to Kanger,[7] when uric acid is administered to cats, there is an increased excretion of it, corresponding to a small per cent of the quantity administered.

According to Burian and Schur,[4] the endogenous as well as the exogenous uric acid can be destroyed by the organism of the dog and cat, for, after kidney extirpation, there is no uric acid found in the blood, and none is excreted into the alimentary canal. We shall see later that the liver of the dog oxidizes uric

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[1] G. Meissner. Beiträge zur Kenntniss des Stoffwechsels im tierischen Organismus. Zeitschr. für rationelle Med., 31, 3, Reihe, 234 (1868).

[2] E. Salkowski. Bildung von Allantoin aus Harnsäure im Tierkörper. Ber. der Dtsch. chem. Gesell., 9, 719 (1876).

[3] R. E. Swain. The Formation of Allantoin from Uric Acid in the Animal Body. Am. Journ. of Physiol., 6, 38 (1901).

[4] A. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. 2. Mitth. Pflüger's Archiv, 87, 239 (1901).

[5] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

[6] H. Spiegelberg. Ueber den Harnsäureeinfarct der Neugeborenen. Arch. für exp. Path. u. Pharmak., 41, 428 (1898).

[7] A. Kanger. Ueber die Möglichkeit einer Steigerung der Harnsäureausscheidung bei Katzen durch Einfuhr reiner Harnsäure per os. Pflüger's Archiv, 100, 428 (1903).

acid. If the liver be cut out of the circulation by tying the blood vessels leading to and from it, then uric acid is found in the blood after kidney extirpation. By giving diuretics, which, according to these authors, increase the rate at which blood is supplied to the kidneys, a greater amount of uric acid escapes oxidation and is excreted.

Oxidation to Allantoin

Allantoin was found by Frerichs and Städeler[1] in the urine of dogs which had breathed chlorine, and in the urine of those animals into whose lungs oil had been introduced. According to the views prevailing at that time, its presence was supposed to be due to deficient oxidation of uric acid. Meissner[2] found it in the urine of dogs after feeding them sodium urate, although there had been no allantoin in the urine previously.

Poduschka[3] and Pohl[4] did not find increased excretion of allantoin after administration of uric acid to dogs. Poduschka performed but one experiment. He did find, however, that from 90 to 91 per cent of the allantoin administered to dogs is excreted unchanged, so that we should expect to find increased amounts of this body in the urine after uric acid feeding, if any is formed from uric acid in the body. Luzzato[5] and Minkowski[6] likewise found that a large part of the allantoin fed to dogs is excreted unchanged.

Salkowski[7] fed 8 grams uric acid to a dog in two days. From the urine he obtained 1.42 grams allantoin by crystallization. This is about 18 per cent of the weight of uric acid given. Swain[8] found that from 10 to 20 per cent of the uric acid fed to dogs appears as allantoin in the urine. According to Salkowski's[9]

[1] F. Frerichs und G. Städeler. Ueber das Vorkommen von Allantoin im Harn bei gestörter Respiration. Müller's Arch. für Anat. und Physiol., 393 (1854).

[2] G. Meissner. Beiträge zur Kenntniss des Stoffwechsels im thierischen Organismus. Zeitschr. für rationelle Med., 31, 3 Reihe, 234 (1868).

[3] R. Poduschka. Quantitative Versuche über Allantoinausscheidung. Arch. für exp. Path. u. Pharmak., 44, 59 (1899).

[4] J. Pohl. Ueber Allantoinausscheidung bei Intoxicationen. Arch. für exp. Path. u. Pharmak., 48, 367 (1902).

[5] A. Luzzato. Ueber das Verhalten des Allantoins im Tierkörper. Zeitschr. für physiol. Chem., 38, 537 (1903).

[6] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

[7] E. Salkowski. Bildung von Allantoin aus Harnsäure im Tierkörper. Ber. der Dtsch. chem. Gesell., 9, 719 (1876).

[8] R. E. Swain. The Formation of Allantoin from Uric Acid in the Animal Body. Am. Journ. of Physiol., 6, 38 (1901).

[9] E. Salkowski. Ueber das Verhalten in das Magen eingeführten Harnsäure im Organismus. Zeitschr. für physiol. Chem., 35, 495 (1902).

indirect method of experiment, a considerable part of the uric acid absorbed is excreted as allantoin.

Mendel and Brown [1] fed 6 and 4½ grams uric acid respectively to two cats and obtained .5 and .3 gram allantoin in the urine, an amount corresponding to about 8 per cent of the uric acid administered. These authors likewise found increased allantoin after the intravenous injection of uric acid and urates in cats and dogs.[2] Kanger [3] found allantoin to the extent of a small per cent of the uric acid fed in the urine of cats.

Those substances which give increased excretion of uric acid in man give increased excretion of allantoin in the dog. Uric acid is probably formed first and then oxidized to allantoin. Thus, Minkowski [4] reported that the administration of thymus to dogs caused the appearance in the urine of a nitrogenous body which he named "urotinsäure." He identified this body later [5] as allantoin.

Cohn [6] likewise found allantoin in the urine of dogs to which calves' thymus had been administered, and Salkowski [7] after feeding pancreas. Minkowski [8] found that nucleic acid also gives allantoin in the urine, and that hypoxanthin is excreted to the extent of about 77 per cent as allantoin; 9-methyladenin also causes a slightly increased excretion of allantoin. The increased excretion of allantoin noticed by Salkowski [9] after a meat diet is probably due to the hypoxanthin in the meat extract.

It is interesting to note that adenin and 7-methyladenin, which give little or no increased excretion of uric acid, according to most authors, when administered free to man, give no allantoin in dogs.

[1] L. Mendel and E. Brown. Observations on the Nitrogenous Metabolism of the Cat, especially in the Excretion of Uric Acid and Allantoin. Am. Journ. of Physiol., 3, 261 (1900).

[2] L. Mendel and B. White. On the Intermediary Metabolism of the Purin Bodies. The Formation of Allantoin in the Animal Body. Am. Journ. of Physiol., 12, 85 (1904).

[3] A. Kanger. Ueber die Möglichkeit einer Steigerung der Harnsäureausscheidung bei Katzen durch Einfuhr reiner Harnsäure per os. Pflüger's Archiv, 100, 428 (1903).

[4] O. Minkowski. Ueber Stoffwechselprodukte nach Thymusfütterung. Verhandl. des 16t Kongr. für innere Med., 271 (1898).

[5] *Ibid.* Ueber Stoffwechselprodukte nach Thymusfütterung. Centralblatt für innere Medizin, 19, 500 (1898).

[6] T. Cohn. Beitrag zur Kenntniss des Stoffwechsels nach Thymusnahrung. Zeitschr. für physiol. Chem., 25, 507 (1898).

[7] E. Salkowski. Ueber das Vorkommen von Allantoin im Harn nach Fütterung mit Pancreas. Centralbl. für med. Wissensch., 36, 929 (1898).

[8] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

[9] E. Salkowski. Ueber das Vorkommen von Allantoin und Hippursäure im Hundeharn. Ber. der Dtsch. chem. Gesell., 11, 500 (1878).

Stadthagen[1] found that guanin, from which little or no uric acid is obtained, when it is administered free to man, gives no allantoin in dogs.

Mendel and Brown[2] found allantoin in the urine of cats after they had fed on thymus and pancreas, and Mendel, Underhill, and White[3] found allantoin in the urine of dogs and cats after the administration of nucleic acid intravenously, intraperitoneally, subcutaneously, per rectum, and by the mouth. The nucleic acid was obtained from wheat embryo.

Borrisow,[4] Poduschka,[5] and Pohl[6] found increased amounts of allantoin in the urine of dogs after hydrazin poisoning. According to Borrisow, the autopsy showed that the liver had been acted upon, and Poduschka noted a degeneration of the nuclei of the liver cells of dogs poisoned with hydrazin. Pohl[6] found that there is no allantoin in the fresh liver or spleen of starving dogs. In the fresh liver and spleen of dogs which had been poisoned with hydrazin he found allantoin. He found also that allantoin is formed when the liver, spleen, thymus, and pancreas of the dog undergo autolysis. He did not find allantoin among the products of autolysis of muscle or blood. These facts taken together seem to indicate that the endogenous uric acid from the nucleoproteid of the body cells, like the exogenous uric acid, is oxidized to allantoin. Thus hydrazin, by causing degeneration of the cell nuclei of the liver, brings about increased excretion of allantoin in the dog, just as phosphorus poison or sulphuric acid injections, by causing degeneration of the liver cells in man, bring about increased excretion of uric acid. Hydroxylamin, which Loewi found to be a general protoplasmic poison especially active in destroying cells, increases the excretion of allantoin in dogs, according to Pohl.[6]

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[1] Stadthagen. Ueber das Vorkommen der Harnsäure in verscheidenen Organen, ihre Verhalten bei Leukämie und die Frage ihrer Entstehung aus den Stickstoffbasen. Virchow's Archiv, 109, 390 (1887).

[2] L. Mendel and E. Brown. Observations on the Nitrogenous Metabolism of the Cat, especially on the Excretion of Uric Acid and Allantoin. Am. Journ. of Physiol., 3, 261 (1900).

[3] L. Mendel, F. Underhill, and B. White. Physiological Studies in Nucleic Acid. Am. Journ. of Physiol., 8, 377 (1903).

[4] P. Borrisow. Ueber die giftige Wirkung des Diamids, des Dibenzoyldiamids und über das Vorkommen des Allantoins im Harn. Zeitschr. für physiol. Chem., 19, 499 (1894).

[5] R. Poduschka. Quantitative Versuche über Allantoinausscheidung. Arch. für exp. Path. u. Pharmak., 44, 59 (1899).

[6] J. Pohl. Ueber Allantoinausscheidung bei Intoxicationen. Arch. für exp. Path. u. Pharmak., 48, 367 (1902).

Oxidation to Oxalic Acid

It is difficult to decide whether or not any oxalic acid is formed by the oxidation of uric acid and the purin bases in the dog. In the first place, it is not fully settled how much of the oxalic acid formed or absorbed by the system is excreted unchanged. Wöhler,[1] the earliest experimenter on this subject, obtained crystals of calcium oxalate in urine after feeding 2 drams of oxalic acid to a dog. Gaglio[2] found oxalic acid in the urine of dogs after administration of from .0005 to .001 gram of oxalic acid, although the urine had previously been free from it. Pohl[3] obtained in the urine practically the whole of the oxalic acid administered after feeding 11.2 and 11.8 milligrams in two cases to a dog. Faust[4] always found in the urine from 92 to 95 per cent of the oxalic acid fed to a dog. The dose varied from .05 to .5 gram.

Auerbach,[5] on the other hand, found only from $4\frac{1}{2}$ to $5\frac{1}{4}$ per cent of the oxalic acid which he fed to dogs in the urine. Guinti,[6] too, found that the greater part of the oxalic acid eaten by dogs is destroyed. Klemperer[7] found that sodium oxalate injected into the circulation of the dog is partly destroyed. Calcium oxalate is not destroyed. According to Abeles,[8] the administration of calcium oxalate per os to dogs does not increase the excretion of oxalic acid. The evidence is somewhat conflicting, but it seems most probable that some, at any rate, of the oxalic acid introduced into the system appears in the urine. Hence, if oxalic acid were formed by the oxidation of uric acid, we should expect a slight increase in its excretion after injection of purin bodies.

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[1] Wöhler. Versuche über den Ubergang von Materien in den Harn. Zeitschr. für Physiol., 1, 125 (1824).

[2] G. Gaglio. Ueber die Unveränderlichkeit des Kohlenoxydes und der Oxalsäure im thierischen Organismus. Arch. für exp. Path. u. Pharmak., 22, 235 (1887).

[3] J. Pohl. Ueber den oxydativen Abbau der Fettkörper im thierischen Organismus. Arch. für exp. Path. u. Pharmak., 37, 413 (1896).

[4] E. Faust. Ueber die Ursachen der Gewohnung an Morphin. Arch. für exp. Path. u. Pharmak., 44, 217 (1900).

[5] A. Auerbach. Zur Kenntniss der Oxydationsprocesse im Thierkörper. Virchow's Archiv, 77, 226 (1879).

[6] L. Guinti. Die Oxydirbarkeit der Oxalsäure im Organismus der Säugethiere und Vogel. Annali di chimica e di farmacologie, 25, 10 (1897), and Maly's Jahresb. über die Fortschritte der Thierchemie, 27, 80 (1897).

[7] G. Klemperer und F. Tritschler. Untersuchungen über Herkunft und Löslichkeit der im Urin ausgeschiedenen Oxalsäure. Zeitschr. für klin. Medizin, 44, 337 (1902).

[8] M. Abeles. Ueber alimentäre Oxalurie. Wiener klin. Wochenschrift, 5, 227 and 296 (1892).

Wöhler and Frerichs,[1] who first directed attention to this point, found a sediment of calcium oxalate in the urine after injection of ammonium urate into a dog. Gallois[2] and Zabelin[3] could not confirm the results of Wöhler and Frerichs. Hammerbacher[4] did not observe an increase in the excretion of oxalic acid after feeding uric acid to dogs.

Salkowski[5] offered as evidence against the theory that oxalic acid can come from uric acid in the dog the fact that dog's liver, which oxidizes uric acid, contains much less oxalic acid than calves' liver, which does not oxidize uric acid. From the fact that there is no relation between the amount of uric acid and the amount of oxalic acid in the dog's urine, Dunlop[6] concluded that uric acid is not oxidized to oxalic acid. Both of these objections are invalid, since oxalic acid may come also from other sources than uric acid.

Swain[7] and Luzzato[8] found a slight increase in the excretion of oxalic acid after feeding uric acid to dogs. This is what we should expect if allantoin is formed from uric acid, for Luzzato[9] has shown that the administration of allantoin brings about a slight increase in the excretion of oxalic acid in dogs.

Oxidation to Parabanic Acid, Alloxan, Alloxantin, and Glycocoll

Parabanic acid, alloxan, and alloxantin are mostly oxidized when given to dogs,[10] so that it is not easy to determine if any of these bodies are formed by the oxidation of uric acid.

[1] F. Wöhler und F. Frerichs. Ueber Veränderungen, welche namentlich organische Stoffe beim ihren Uebergang in den Harn erfahren. Annal. d. Chem. u. Pharm., 65, 335 (1848).

[2] Gallois. Experiences sur l'urée et les urates. Comptes rendus, 44, 734 (1857).

[3] Zabelin. Ueber die Umwandling der Harnsäure im Thierkörper. Annal. d. Chem. u. Pharm., 2 Suppl., 326 (1863).

[4] L. Hammerbacher. Zur Physiologie der Oxalsäure. Pflüger's Archiv, 33, 89 (1884).

[5] E. Salkowski. Ueber Entstehung und Ausscheidung der Oxalsäure. Berl. klin. Wochenschrift, 37, 434 (1900).

[6] J. Dunlop. The Excretion of Oxalic Acid in Urine, and its Bearing on the Pathological Condition Known as Oxaluria. The Journal of Pathology and Bacteriology, 3, 389 (1894–5).

[7] R. Swain. The Formation of Allantoin from Uric Acid in the Animal Body. Am. Journ. of Physiol., 6, 38 (1901).

[8] A. Luzzato. Ueber das Verhalten des Allantoins im Tierkörper. Zeitschr. für physiol. Chem., 38, 537 (1903).

[9] *Ibid.* Zur Physiologie der Oxalsäure im Harn. Zeitschr. für physiol. Chem., 37, 225 (1903).

[10] Koehne. Ueber das Verhalten einiger Säureamide im tierischen Organismus. Inaug. Dissert., Rostock (1894), *and* Maly's Jahresb. über die Fortschritte der Thierchemie, 24, 83 (1894).

A repetition, on dogs, of Wiener's work on the formation of glycocoll from uric acid in rabbits would not be of any value, for Bunge and Schmiedeberg [1] have shown that, in the dog, hippuric acid is synthesized only in the kidneys. Further, Schmiedeberg [2] and Minkowski [3] have shown that after the hippuric acid is synthesized, it is again partly decomposed into benzoic acid and glycocoll by a ferment.

Summary

The evidence, then, seems in favor of the view that, in the dog, the endogenous and exogenous uric acid is excreted in very small part as uric acid. The greater portion seems to be destroyed. A part, the size of the fraction is not settled, is oxidized to allantoin. The larger part of the allantoin is excreted unchanged. A small part is further oxidized and excreted partly as oxalic acid and urea.

IN MAN

Early Work

Half a century ago it was believed that uric acid is normally oxidized to urea. According to Liebig,[4] uric acid is oxidized to urea and oxalic acid in man. Wöhler and Frerichs [5] obtained calcium oxalate sediment and increased excretion of urea in the urine of men to whom ammonium urate had been fed. Stokvis [6] also noticed an increased excretion of urea after eating uric acid. Neubauer [7] found oxalate sediment in the urine when uric acid had been administered the night before. He believed that the presence of the oxalate is an indication of the retardation of the oxidation processes during sleep, that in

[1] G. Bunge und O. Schmiedeberg. Ueber die Bildung der Hippursäure. Arch. für exp. Path. u. Pharmak., 6, 233 (1876).

[2] O. Schmiedeberg. Ueber die Spaltungen und Synthesen im Tierkörper. Arch. für exp. Path. u. Pharmak., 14, 379 (1881).

[3] O. Minkowski. Ueber Spaltungen im Thierkörper. Arch. für exp. Path. u. Pharmak., 17, 445 (1883).

[4] J. Liebig. Animal Chemistry or Organic Chemistry in its Application to Physiology and Pathology. Transl. by W. Gregory. Ed. by W. Webster (1843).

[5] F. Wöhler und F. Frerichs. Ueber Veränderungen, welche namentlich organische Stoffe bei ihrem Uebergang in den Harn erfahren. Annal. d. Chem. u. Pharm., 65, 335 (1848).

[6] B. Stokvis. Bijdragen tot de physiologie van het acidum uricum. Ned. Tijdschr., 3, 587, und 607 Afl., Oct. (1859). Arch. f. d. holl. Beitr., 2, 260 (1860), and Schmidt's Jahresb., 109, 4 (1861).

[7] C. Neubauer. Ueber die Zersetzung der Harnsäure im Thierkörper. Annal. d. Chem. u. Pharm., 99, 206 (1856).

the daytime the oxalic acid would be oxidized to carbon dioxide and water. Gallois [1] noticed in one case a sediment of calcium oxalate after administration of potassium urate to a man, and Furbringer [2] also sometimes found an increased sediment of oxalate after administration of ammonium urates to man. We know now that the presence of a sediment of calcium oxalate in the urine does not necessarily indicate large amounts of oxalate in the urine. The occurrence of an oxalate sediment, like the occurrence of a urate sediment, depends on other factors. In the method of determining the urea used by these early authors, uric acid, creatin, and other nitrogenous bodies were also determined. Their conclusions, therefore, are of no value.

Excretion as Uric Acid

Until very recently, it has been believed that the human organism possessed the power of destroying uric acid introduced from without. Garrod [3] did not find that the administration of uric acid caused an increased excretion of uric acid. Weintraud [4] could not observe an increased excretion of uric acid after feeding 4 to 6 grams, or Weiss [5] after feeding 10 grams to men. The question of whether or not the acid was absorbed was not considered.

According to Mitscherlich,[6] on the other hand, uric acid is not destroyed by the organism. Haig [7] found about three fourths of the uric acid which he ate in the urine. He used, however, an inaccurate method for the determination of uric acid, and his results were further vitiated by the fact that he was taking also sodium salicylate, a drug which increases the excretion of uric acid.

According to Loewi,[8] all the uric acid introduced into the body

[1] Gallois. Expériences sur l'urée et les urates. Comptes rendus, 44, 734 (1857).

[2] P. Furbringer. Zur Oxalsäure Ausscheidung durch den Harn. Deutsche Arch. für klin. Medizin, 18, 143 (1876).

[3] H. Garrod. Uric Acid: Its Physiology and its Relation to Renal Calculi and Gravel. Brit. Med. Journ., 1, 547 (1883).

[4] Weintraud. Ueber Harnsäure im Blute und ihre Bedeutung für die Entstehung der Gicht. Wiener klin. Rundschau, 10, 3 (1896).

[5] J. Weiss. Weitere Beiträge zur Erforschung der Bedingungen der Harnsäurebildung. Zeitschr. für physiol. Chem., 27, 217 (1899).

[6] Mitscherlich. De acidi oxalici, etc., effectu in animalibus observatis. Inaug. Dissert., Berl. (1845).

[7] Haig. On Uric Acid as a Factor in Causation of Disease. London (1896).

[8] O. Loewi. Beiträge zur Kenntniss des Nukleinstoffwechsels. 1. Mitth. Arch. für exp. Path. u. Pharmak., 44, 1 (1901).

is excreted unchanged. To three men who were living on a standard diet, he fed thymus. The increased excretion of P_2O_5 after the addition of thymus to the diet, according to Loewi, is a measure of the amount of nucleins absorbed and oxidized. Since, in all three cases, he found that the ratio of the increased excretion of P_2O_5 to the increased excretion of uric acid is the same, he concluded that all the uric acid formed from the purin bases of the thymus is excreted unchanged, for otherwise it would be necessary to assume that the different individuals form the same amount of uric acid and destroy the same amount. Further, according to Loewi, if we use Schindler's [1] determinations of the amount of purin bodies in thymus, the amount of uric acid in the urine after thymus feeding will correspond quantitatively to the purin bases ingested.

As we have seen in an earlier part of this work, the increased excretion of P_2O_5 after thymus feeding is not a measure of the amount of nuclein absorbed and excreted. Further, Burian and Schur [2] have shown that the ratio of the increased excretion of P_2O_5 to the increased excretion of uric acid is not the same in different individuals. And, finally, the best determinations of the amount of purin bases in thymus show that Schindler's figures are far too low.[3]

Burian and Schur [4] injected uric acid into a man and found that about 50 per cent is excreted unchanged. It will be remembered that they found about 50 per cent of the hypoxanthin given in the food is excreted as uric acid. It seems probable, then, that practically the whole of the hypoxanthin must be oxidized to uric acid, and that about one half of this uric acid is oxidized and about one half excreted unchanged.

Oxidation to Oxalic Acid

It is difficult to say in what way uric acid is oxidized in the body of man. In regard to oxalic acid, it is not fully settled just

[1] S. Schindler. Beiträge zur Kenntniss des Adenins, Guanins, und ihrer Derivate. Zeitschr. für physiol. Chem., 13, 432 (1889).

[2] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. 1. Mitth. Pflüger's Archiv, 80, 241 (1900).

[3] *Ibid. Also*

R. Burian und J. Hall. Die Bestimmung der Purinstoffe in tierschen Organen mittels der Methode des korrigierten wertes. Zeitschr. für physiol. Chem., 38, 336 (1903).

[4] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsels. 2. Mitth. Pflüger's Archiv, 87, 239 (1901).

what fraction of this is destroyed when it is introduced into the body.

After the administration of oxalic acid and oxalates, calcium oxalate was found in the urinary sediment by Duckworth,[1] and by Rabuteau.[2] Buchheim [3] fed oxalic acid and sodium oxalate to man and found from 8 to 14 per cent unchanged in the urine. According to Rotter,[4] small amounts of oxalic acid are excreted completely unchanged. According to Abeles,[5] small amounts of oxalic acid are oxidized completely in the body. Large amounts bring about intestinal disturbances which cause oxaluria, and this explains the presence of oxalic acid in the urine after administration of large amounts.

Marfori,[6] Giunti,[7] Lommel,[8] and Klemperer and Tritschler [9] found that a small part only of the oxalic acid in the food is excreted unchanged. Pierallini [10] found that a small per cent of the oxalic acid of the food is excreted unchanged.

Esbach [11] swallowed 5 grams oxalic acid and found .181 gram or 3.6 per cent in the urine. Dunlop [12] gave .6 gram oxalic acid to each of two men and found respectively .024 and .015 gram, or 4 per cent and 2.5 per cent in the two urines. In another experiment,[13] he fed .6 gram oxalic acid to a man and found 3.6

[1] D. Duckworth. Notes on Oxaluria. St. Barth. Hosp. Rec., London, 2, 160 (1866).

[2] Rabuteau. Contribution à l'étude du mode d'élimination et des effets toxiques de l'acide oxalique et des oxalates. Gazette méd. de Paris, 4th ser., 3, 74 (1874).

[3] Buchheim. Ueber den Uebergang einiger organischen Säuren in den Harn. Arch. f. physiol. Heilk., Neue Folge, 1, 122 (1857).

[4] Rotter. Footnote in Wiener's article, Ueber Zersetzung und Bildung der Harnsäure im Thierkörper. Arch. für exp. Path. u. Pharmak., 42, 379 (1899).

[5] M. Abeles. Ueber Alimentaire Oxalurie. Wien. klin. Wochenschrift, 5, 277 und 296 (1892).

[6] P. Marfori. Sulle tranzformazioni di alcuni acidi della serie ossalica nell' organismo dell' uomo. Annali de chimica e di farmacologica, 12, 250 (1890), and Maly's Jahresb. über die Fortschritte der Thierchemie, 20, 90 (1890).

Ibid. Ueber das Verhalten der Oxalsäure im Organismus. Annali di chimica e di farmacologica, 25, fasc. 5 (1897), and Maly's Jahresb. über die Fortschritte der Thierchemie, 27, 80 (1897),

[7] L. Giunti. Die Oxydirbarkeit der Oxalsäure im Organismus der Säugetiere und Vögel. Annali di chimica e di farmacologia, 25, 10 (1897), and Maly's Jahresb. über die Fortschritte der Thierchemie, 27, 80 (1897).

[8] F. Lommel. Ueber die Herkunft der Oxalsäure im Harn. Deutsche Arch. für klin. Medizin, 63, 599 (1899).

[9] G. Klemperer und F. Tritschler. Untersuchungen über Herkunft und Löslichkeit der im Urin ausgeschiedenen Oxalsäure. Zeitschr. für klin. Medizin, 44, 337 (1902).

[10] G. Pierallini. Ueber alimentare Oxalsäure. Virchow's Archiv., 160, 173 (1900).

[11] G. Esbach. L'oxalurie. Bull. gén. der therap. medicale et chirurgicale, Paris, (1883).

[12] J. Dunlop. The Excretion of Oxalic Acid in Urine, and Its Bearing on the Pathological Condition known as Oxaluria. Journ. of Path. and Bact. 3, 389 (1894–5).

[13] *Ibid.* Reports from the Laboratory of the Royal College of Physicians, Edinburgh (1897).

per cent of it in the urine. About 3 per cent of the oxalic acid administered to a man by Stradomsky [1] was found again in the urine. It seems most probable, then, that about 3 or 4 per cent of the oxalic acid administered per os is excreted unchanged in the urine. A larger fraction of the oxalic acid absorbed into the system would probably be excreted unchanged, for, according to Stradomsky,[1] about 33 per cent of the oxalic acid which he fed to a man was found again in the feces, and Klemperer and Tritschler [2] found that when oxalic acid is injected into the circulation a considerable part of it is excreted unchanged. It seems very likely that if uric acid is oxidized to oxalic acid in the body, the administration of uric acid or purin bodies would occasion an increased excretion of oxalic acid.

There is no direct evidence that uric acid is oxidized to oxalic acid in man. Klemperer and Tritschler [2] fed uric acid to a man, but did not find that the excretion of oxalic acid was increased. Garrod [3] had observed that a blood serum rich in uric acid gave calcium oxalate crystals on putrefaction, and had based his view that uric acid is oxidized to oxalic acid in the body on that fact. Klemperer and Tritschler [2] made a similar observation. They found that when uric acid is mixed with fresh blood, the uric acid disappears and oxalic acid appears.

Mills [4] and Stradomsky [1] noticed that the largest amount of oxalic acid is found in the urine after a meat diet. Bunge [5] denied that this is so. This increased amount of oxalic acid has been attributed to the purin bases in the meat extract, especially in view of the fact that Dunlop [6] has found that there is no oxalic acid in the urine after a milk diet, and that Salkowski,[7] Stradomsky,[1] and Lommel [8] have found that addition of

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[1] N. Stradomsky. Die Bedingungen der Oxalsäurebildung im menschlichen Organismus. Virchow's Archiv, 163, 404 (1901).

[2] G. Klemperer und F. Tritschler. Untersuchungen über Herkunft und Löslichkeit der im Urin augeschiedenen Oxalsäure. Zeitschr. für klin. Medizin, 44, 337 (1902).

[3] A. Garrod. The Nature and Treatment of Gout and Rheumatic Gout. London (1859).

[4] W. Mills. Ueber die Ausscheidung der Oxalsäure durch den Harn. Virchow's Archiv, 99, 305 (1885).

[5] G. Bunge. Lehrbuch der physiologische Chemie.

[6] J. Dunlop. The Excretion of Oxalic Acid in Urine, and Its Bearing on the Pathological Condition known as Oxaluria. Journ. of Path. and Bact. 3, 389 (1894–5).

[7] E. Salkowski. Ueber Entstehung und Ausscheidung der Oxalsäure. Berl. klin. Wochenschrift, 37, 434 (1900).

[8] F. Lommel. Ueber die Herkunft der Oxalsäure im Harn. Deutsche Arch. für klin. Medizin, 63, 599 (1899).

large amounts of pure proteid to the diet does not increase the excretion of oxalic acid. The increased excretion of oxalic acid after meat diet may be due to something other than the purin bases, however. Klemperer and Tritschler [1] have found that creatinin, and Lommel,[2] Mohr and Salomon,[3] and Stradomsky [4] that gelatin, both of which are found in meat, increases the excretion of oxalic acid.

According to Salkowski [5] and Lommel,[2] the addition of thymus to the food causes an increased excretion of oxalic acid. Stradomsky [4] and Lüthje,[6] on the other hand, fed thymus, and Mohr and Salomon [3] fed both thymus and pancreas to men, but observed no increased excretion of oxalic acid. Even if thymus does cause an increased excretion of oxalic acid, it is not necessarily an indication that the oxalic acid comes from uric acid. Cippolina [7] has found that there is more oxalic acid in the thymus than in the other organs. Further, gelatin and other substances may be the source of the oxalic acid, and in this case Kutscher and Schenck [8] believe that oxaminic acid, which they obtained in the oxidation of gelatin by calcium permanganate, is the source of the oxalic acid.

Cippolina [7] believes that the human liver can oxidize uric acid to oxalic acid. He found more oxalic acid in human liver that had been allowed to undergo autodigestion after addition of uric acid than in liver to which uric acid had not been added.

According to Wiener,[9] his work on the synthesis of uric acid from certain of the dibasic aliphatic acids indicates that a relation between the uric acid and oxalic acid of the urine might be ex-

[1] G. Klemperer und F. Tritschler. Untersuchungen über Herkunft und Löslichkeit der im Urin ausgeschiedenen Oxalsäure. Zeitschr. für klin. Medizin, 44, 337 (1902).

[2] F. Lommel. Ueber die Herkunft der Oxalsäure im Harn. Deutsche Arch. für klin. Medizin, 63, 599 (1899).

[3] L. Mohr und H. Salomon. Untersuchungen zur Physiologie und Pathologie der Oxalsäurebildung- und ausscheidung beim Menschen. Deutsche Arch. für klin. Medizin, 70, 486 (1901).

[4] N. Stradomsky. Die Bedingungen der Oxalsäurebildung im menschlichen Organismus. Virchow's Archiv, 163, 404 (1901).

[5] E. Salkowski. Ueber die Bestimmung der Oxalsäure und das Vorkommen von Oxalsäure im Harn. Zeitschr. für physiol. Chem., 29, 436 (1900).

[6] H. Lüthje. Zur physiologischen Bedeutung der Oxalsäure. Zeitschr. für klin. Medizin, 35, 271 (1898).

[7] Cippolina. Ueber die Oxalsäure im Organismus. Berl. klin. Wochenschrift, 38, 544 (1901).

[8] F. Kutscher und M. Schenck. Zur Kenntnis der Oxalurie. Zeitschr. für physiol. Chem., 43, 337 (1904).

[9] H. Wiener. Ueber synthetische Bildung der Harnsäure im Thierkörper. Verhandl. des 19t Kongr. für innere Med., 383 (1901), and Hofmeister's Beiträge, 2, 42 (1902).

pected, and it is not necessary to assume that uric acid is decomposed to oxalic acid, for certain of these acids are partly synthesized to uric acid and partly oxidized to oxalic acid. But, as we have seen, it is doubtful if any uric acid is formed in man by synthesis. Another point to be taken into consideration is the fact that the oxalic acid found in the urine may not have been excreted as such. According to Luzzato[1] and Salkowski,[2] the oxalic acid of the urine increases on standing, and may be formed from other bodies found in the urine.

Oxidation to Allantoin and Glycocoll

If allantoin were formed in man by the oxidation of uric acid, we should expect to find it in the urine. Only Wöhler and Frerichs[3] found allantoin completely destroyed in man. Loewi[4] fed allantoin to a man and found a small part unchanged in the urine. Minkowski[5] found in the urine about 20 per cent, and Poduschka[6] from 30 to 50 per cent of the allantoin they fed to men.

Minkowski[5] and Loewi[7] fed thymus to men, but did not find allantoin in the urine. Loewi[4] found no allantoin in the urine after feeding nuclein to man.

No attempts have been made to find out if glycocoll is formed by the oxidation of uric acid in man.

Summary

In man, then, about half the uric acid introduced into the circulation is oxidized. It is not known what compounds are formed by the oxidation of the uric acid.

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[1] A. Luzzato. Zur Physiologie der Oxalsäure und Oxalsäure im Harn. Zeitschr. für physiol. Chem., 37, 225 (1903).

[2] E. Salkowski. Zur Kenntnis des Harns und des Stoffwechsels der Herbivoren. Vorkommen von Allantoin Indikanbestimmung. Zeitschr. für physiol. Chem., 42, 213 (1904).

[3] F. Wöhler und F. Frerichs. Ueber Veränderungen, welche namentlich organische Stoffe bei ihrem Übergang in den Harn erfahren. Annal. d. Chem. u. Pharmak., 65, 335 (1848).

[4] D. Loewi. Beiträge zur Kenntniss des Nukleinstoffwechsels. 1. Mitth. Arch. für exp. Path. u. Pharmak., 44, 1 (1901).

[5] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharmak., 41, 375 (1898).

[6] R. Poduschka. Quantitative Versuche über Allantoinausscheidung. Arch. für exp. Path. u. Pharmak., 44, 59 (1899).

[7] Loewi. Beiträge zum Nukleinstoffwechsel. Sitzungsber. der Gesell. zur Beförderung der gesammten Naturwissensch., Marburg, 120 (1899).

The Organ of Formation of Uric Acid

The question of the organ in which uric acid is formed in the body has caused a very great amount of controversy. Different authors have believed that the liver, spleen, kidneys, cartilage of the joint, the cells of the intestinal tract, and the muscles form the uric acid. Until it was understood that in birds uric acid is formed chiefly by synthesis, and in mammals chiefly by the oxidation of purin bases, many authors had believed that theories based on the work of Strahl and Lieberkühn, Zalesky, Chrzonszczewsky, Meissner, Pawlinoff, v. Schröder, Colasanti, and others on the formation of uric acid in birds and snakes could be applied in mammals. The work on birds has been discussed in another place, and as we now know that the metabolism of uric acid is different in birds and mammals, it will not be necessary to consider it at this point. The erroneous ideas concerning the source and behavior of uric acid in mammals have likewise led to many wrong views concerning the organ in which it is formed. The mistake of applying the facts observed in one mammal to mammals in general, the use of inaccurate methods of analysis, and the misinterpretation of the facts which have been discovered, have caused as much confusion in this subject as in the study of the metabolism of uric acid. The views of the different authors will first be presented, and then considered from the standpoint of our present knowledge of the metabolism of uric acid.

THE KIDNEYS

Hoppe-Seyler[1] believed that the uric acid excreted is only that part which is formed in the kidneys. According to this author, uric acid is oxidized in the body, so that if any is formed by other organs, it is destroyed before reaching the kidneys. We now know that uric acid is not completely destroyed in the body, that a fraction of the uric acid formed in other parts of the body can reach the kidneys unchanged.

It has also been stated that the blood does not contain uric acid, and that therefore the uric acid in the urine must be formed where the urine is formed, — in the kidneys. Yet Garrod[2] and

[1] F. Hoppe-Seyler. Physiologische Chemie. Berlin (1881).

[2] A. Garrod. Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism, and Bright's Disease. Medico-Chirurgical Transactions, 31, 83 (1848).

Abeles [1] have found uric acid in normal human blood in health. Weintraud [2] found uric acid in normal human blood after a meal containing thymus, and Abeles [1] likewise found it in a number of normal human organs. v. Jaksch [3] and Klemperer [4] did not find any uric acid in the blood of normal individuals, but they, and also Garrod, Kam,[5] and Magnus-Levy [6] did find it in the blood of persons suffering from certain diseases. The blood does contain uric acid therefore, though perhaps at times in such small quantities as to be difficult to detect.

Strahl and Lieberkühn [7] stated that they found uric acid in the blood of cats whose kidneys had been extirpated. They looked upon this as proof that uric acid is not formed in the mammal kidney. Burian and Schur [8] have failed to confirm Strahl and Lieberkühn's observation. As we shall see later, we should not expect to find uric acid in the blood of cats and dogs even after kidney extirpation, so that this work has no bearing on the facts in man in either case.

Dickinson,[9] Bartels,[10] Fleischer,[11] and Wagner [12] found the excretion of uric acid decreased in nephritis. This was looked upon as evidence that the kidneys produce uric acid, and that there is a decreased production of uric acid when the kidneys are

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[1] M. Abeles. Ueber Harnsäure im Blute und einigen Organen und Geweben. Wiss. med. Jahrb., 83, 479 (1887), and Jahresb. über die Leistung und Fortschritte in die gesammte Medicin, 1, 130 (1887).

[2] W. Weintraud. Ueber Harnsäure im Blute und ihre Bedeutung für die Entstehung der Gicht. Wien klin. Rundschau, 16, 3 (1896).

[3] R. v. Jaksch. Ueber die klinische Bedeutung des Vorkommen von Harnsäure und Xanthinbasen im Blute, den Exudaten und Transudaten. Prager Festschrift, 79 (1870), and Zeitschr. für Heilkunde, 11, 415 (1891), also Ueber Uricacidaemie. Deutsche med. Wochenschrift, 16, 741 (1890).

[4] G. Klemperer. Zur Pathologie und Therapie der Gicht. Deutsche med. Wochenschrift, 21, 655 (1895).

[5] B. Kam. Bijdragen tot de kennis der urinezuuruitscheidung. Diss. Leiden (1898). Maly's Jahresb. über die Fortschritte der Thierchemie, 28, 573 (1898).

[6] A. Magnus-Levy. Ueber den Stoffwechsel bei acuter und chronischer Leukämie. Virchow's Archiv, 152, 107 (1898).

[7] Strahl und Lieberkühn. Harnsäure im Blute und einige neue Bestantheile des Urins. Berlin (1848). Jahresber. über die Fortschritte in der gesammten Medicin (1848).

[8] Burian und Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. 2. Mitth. Pflüger's Archiv, 87, 239 (1901).

[9] W. Dickinson. Diseases of the Kidneys and Urinary Derangements. London (1875).

[10] Bartels. Nierenkrankheiten. Ziemssen's Handbuch der spec. Pathol. und Therapie, IX, 1 (1877).

[11] R. Fleischer. Klinische und pathologisch-chemische Beiträge zur Lehre von den Nierenkrankheiten. Deutsche Arch. für klin. Medizin, 29, 129 (1881).

[12] E. Wagner. Der Morbus Brightii. Ziemssen's Handbuch der spec. Pathol. und Therapie, IX, 1 (1882), 3 Aufl., p. 18.

diseased. Becquerel,[1] Gorup-Besanez,[2] Frerichs,[3] Stadthagen,[4] and Van Ackeren,[5] on the other hand, found the excretion of uric acid normal, and Vogel[6] found it even high, so that decreased excretion of uric acid could not be considered a constant symptom of nephritis, even before the more accurate work of recent times.

In 1895, Krüger and Wulff[7] published their method for the determination of the purin bodies in the urine. By use of this method, Kolisch and Dostal[8] found that the excretion of the purin bodies as a whole is normal in nephritis. The excretion of uric acid is decreased and that of purin bases is increased. According to these authors, uric acid is formed normally in the kidneys from the nucleins. A small part only of the nucleins become excreted as purin bases. In nephritis, the action of the kidney is impaired so that less uric acid is formed. A greater part of the nucleins are excreted as purin bases. Only Fodor[9] and Baginsky and Sommerfeld[10] confirmed Kolisch and found that the ratio of the quantity of uric acid to the quantity of purin bases in the urine is decreased in nephritis.

Unfortunately, Kolisch and Dostal, Fodor, and Baginsky and Sommerfeld all used the Krüger-Wulff method for the determination of purin bodies in the urine. As we have already seen,

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[1] Becquerel. Semiotique des urines ou traité des alterations de l'urine dans les maladies suivi d'un traité de la maladie de Bright. Paris, 509 (1841).

[2] Gorup-Besanez. Arch. für Physiol. Heilk., 8, 712 (1859).

[3] Frerichs. Die Bright'sche Nierenkrankheit und deren Behandlung. Braunschweig (1851).

[4] M. Stadthagen. Ueber das Vorkommen von Harnsäure in verscheidenen thierischen Organen, ihr Verhalten bei Leukämie und die Frage ihrer Entstehung aus den Stickstoffbasen. Virchow's Archiv, 109, 390 (1887).

[5] F. Van Ackeren. Ueber Harnsäureausscheidung bei einigen Krankheiten in besondere bei Morbus Brightii. Charité Annalen, 17, 206 (1892).

[6] Vogel. Krankheiten der harnbereitendes Organ. Virchow's Handbuch der spec. Pathol. und Therapie, IV, 2, Erlangen (1856–1865).

[7] M. Krüger und C. Wulff. Ueber eine neue Methode zur quantitativen Bestimmung der sogenannten Xanthinkörper im Harne. Zeitschr. für physiol. Chem., 20, 176 (1895).

[8] R. Kolisch und H. Dostal. Das Verhalten der Alloxurkörper in pathologischen Harnen. Wien klin. Wochenschrift, 8, 413, and 435 (1895).

R. Kolisch. Ueber Verhalten der Alloxurkörper im Harn bei Nephritis. Wiener med. Blatter, 19, 117 (1896).

[9] G. Fodor. Ueber das Verhalten der Harnsäure bei Nephritis. Centralblatt für innere Medizin, 16, 865 (1895).

[10] A. Baginsky und Sommerfeld. Ueber Ausscheidung von Xanthinkörper bei Nephritis. Verhandl. der Berlin. physiologisch. Gesell., 1895. Du Bois Arch. für Physiol., 562 (1895).

A. Baginsky. Ueber das Vorkommen von Xanthin, Guanin, und Hypoxanthin. Zeitschr. für physiol. Chem., 8, 395 (1884).

Weintraud,[1] Zülzer,[2] Laquer,[3] Huppert,[4] Salkowski,[5] and Flatow and Reitzenstein[6] have shown that this method is very unreliable. The presence of albumin in the urine, as in cases of nephritis, would affect the results so as to show apparently high purin bases.

Ascoli,[7] Rommel,[8] Martin,[9] Albu,[10] and Magnus-Levy[11] have found the excretion of purin bodies normal in nephritis. Magnus-Levy,[11] Albu,[10] and Ascoli[7] found the amount of uric acid in the urine normal in nephritis, and Laquer[12] and Martin[13] found it often normal. Rommel[8] and Zülzer[14] found the excretion of uric acid normal and often high in nephritis. v. Noorden,[15] Zülzer,[14] and Martin[13] found that the ratio of the amount of uric acid to the amount of purin bases is normal in nephritic urine. Kam[16] found the uric acid sometimes high, sometimes normal, and sometimes low. Schmoll[17] found after feeding nuclein, and Kam,[16]

[1] Weintraud. Beiträge zum Stoffwechsel der Gicht. Charité Annalen, 215 (1895).

[2] G. Zülzer. Ueber die Alloxurkörperausscheidung im Harne bei Nephritis. Berl. klin. Wochenschrift, 33, 72 (1896).

[3] B. Laquer. Ueber die Krüger-Wulffsche Methode der Alloxurkörperbestimmung. Centralblatt für innere Medizin, 17, 1129 (1896).

[4] H. Huppert. Ueber die Bestimmung der Xanthinbasen nach Krüger-Wulff. Zeitschr. für physiol. Chem., 22, 556 (1897).

[5] E. Salkowski. Ueber die Krüger-Wulffsche Methode zur Bestimmung der Alloxurkörper im Harne. Deutsche med. Wochenschrift, 23, 213 (1897).

[6] R. Flatow und A. Reitzenstein. Zur Xanthinbasenbestimmung im Urin. Deutsche med. Wochenschrift, 32, 354 (1897).

[7] G. Ascoli. Sul comportamento dei corpi allossurici nelle nefriti. Clinica med., 1898. Maly's Jahresb. über die Fortschritte der Thierchemie, 29, 722 (1899).

[8] O. Rommel. Die Ausscheidung der Alloxurkörper bei Gicht und Schrumpfniere. Zeitschr. für klin. Medizin, 30, 200 (1896).

[9] C. Martin. Ueber das Ausscheidungsverhältnisse der Alloxurkörper bei Nephritis. Centralblatt für innere Medizin, 20, 625 (1899); and Maly's Jahresb. über die Fortschritte der Thierchemie, 29 (1899).

[10] Albu. Discussion of Laquer's Article: Ueber die Ausscheidungsverhältnisse der Alloxurkörper im Harne von Gesunden und Kranken. Verhandl. des 14t Kongr. für innere Med., 423 (1896).

[11] A. Magnus-Levy. Discussion of Laquer's Article: Ueber die Ausscheidungsverhältnisse der Alloxurkörper im Harne von Gesunden und Kranken. Verhandl. des 14t Kongr. für innere Med., 423 (1896).

[12] B. Laquer. Ueber die Ausscheidungverhältnisse der Alloxurkörper im Harne von Gesunden und Kranken. Verhandl. des 14t Kongr. für innere Med., 333 (1896).

[13] C. Martin. Ueber die Ausscheidungsverhältnisse die Alloxurkörper bei Nephritis. Centralblatt für innere Medizin, 20, 625 (1899).

[14] G. Zülzer. Ueber die Alloxurkörperausscheidung im Harn bei Nephritis. Berl. klin. Wochenschrift, 33, 72 (1896).

[15] v. Noorden. Discussion of Laquer's Article: Ueber die Ausscheidungsverhältnisse der Alloxurkörper im Harne von Gesunden und Kranken. Verhandl. des 14t Kongr für innere Med., 420 (1896).

[16] B. Kam. Bijdragen tot de kennis der urinezuuruitscheidung. Diss. Leiden (1898). Maly's Jahresb. über die Fortschritte der Thierchemie, 28, 573 (1898).

[17] E. Schmoll. Stoffwechselversuch an einem Gichtkranken. Zeitschr. für klin. Medizin, 29, 510 (1896).

and Zagari and Pace [1] after thymus feeding, that there is increased excretion of uric acid just as in health. There seems no reason, then, to assume that in nephritis we have abnormal quantities of uric acid or purin bodies in the urine. Malfatti [2] could not obtain uric acid from purin bases by passing blood containing purin bases through an isolated kidney, or by allowing the kidney of a calf to act upon the purin bases in spleen extract.

There is, therefore, no indication that uric acid is formed in the kidneys.

THE SPLEEN

Scherer,[3] Cloetta,[4] and Gorup-Besanez [5] found uric acid in ox spleen, and Scherer [6] found it in the spleen of a man who had leukemia. Virchow [7] observed increased uric acid sediment in the urine and uric acid concretions in cases of leukemia, and Ranke [8] found the excretion of uric acid increased. These facts led Virchow [7] to believe that the uric acid might come from the spleen, and led Ranke [8] to state that uric acid is formed in the spleen.

Only Abeles [9] has since found uric acid in the fresh human spleen, and Stokvis [10] in the spleen of a calf. Salomon,[11] Salkowski,[12]

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[1] G. Zagari e D. Pace. La genesi dell' acido urico e la gotta in riguardo alla patogenesi e al' indirizzo terapeutico. Centralblatt für innere Medizin, 19, 816 (1898).

[2] H. Malfatti. Ueber die Alloxurkörper und ihr Verhältnisse zur Gicht. Wien klin. Wochenschrift, 9, 723 (1896).

[3] Scherer. Ueber einen im thierischen Organismus vorkommenden dem Xanthinoxydverwandten Körper. Ann. der Chem. u. Pharm., 73, 328 (1850).

[4] A. Cloetta. Ueber das Vorkommen von Inosit, Harnsäure, etc., im thierschen Körper., Ann. der Chem. u. Pharm., 99, 289 (1856).

[5] E. v. Gorup-Besanez. Ueber die chemischen Bestandtheile einiger Drüsensäfte. Ann. der Chem. u. Pharm., 98, 1 (1856).

[6] Scherer. Untersuchungen über das Blut bei Leukämie. Verhandl. d. physik. Mediz. Gesellsch. zu Wurzburg, 2, 321 (1851).

Ibid. Beitrag zur Geschichte der Leukämie. Chemische Untersuchungen des Blutes. Verhandl. d. physik. Mediz. Gesellsch. zu Wurzburg, 7, 123 (1856).

[7] R. Virchow. Zur pathologischen Physiologie des Blutes. Virchow's Archiv, 5, 43 (1853).

[8] H. Ranke. Beobachtungen und Versuche über die Ausscheidung der Harnsäure beim Menschen (1858).

[9] M. Abeles. Ueber Harnsäure im Blute und einigen Organen und Gewebe. Wien med. Jahrb., 83, 479 (1887), and Jahresb. über die Fortschritte der gesammten Medicin, 1, 130 (1887).

[10] B. Stokvis. Bijdragen tot de physiologie van het acidum uricum. Ned. Tijdschr., 3, p. 587, Afl., Oct., 1859, Arch. f. d. holl., Beitr., p. 260 (1860); Schmidt's Jahrb., 109, 4 (1861).

[11] Salomon. Arch. f. Physiol., 762 (1876).

[12] E. Salkowski. Chemische untersuchungen von Leber und Milz in einen Fall von lienaler Leukämie. Virchow's Archiv, 81, 166 (1880).

and Bockendahl and Landwehr [1] found no uric acid in leukemic spleen.

An absolute increased excretion of uric acid in leukemia has been found also by Berell,[2] Bohland and Schurz,[3] Hoffmann,[4] Fleischer and Penzoldt,[5] Sticker,[6] Ebstein,[7] Magnus-Levy,[8] Zagari and Pace,[9] and in one case by Galdi.[10] An increase in the ratio, *uric acid : urea*, has been found by Parkes,[11] Jacubasch,[12] Hoffmann,[4] Reichardt,[13] and Schmuziger.[14] An increased excretion of purin bases was found in leukemia by Bondzynski and Gottlieb,[15] and by Kolisch and Dostal.[16] Bondzynski and Gottlieb and Kolisch and Dostal [16] used the Krüger-Wulff method of determination.

The work of Giacosa [17] and Horbaczewski,[18] who found that uric acid is formed by the autolysis of ox spleen, and the work of

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[1] A. Bockendahl und H. Landwehr. Chemische Untersuchungen leukämischen Organen. Virchow's Archiv, 84, 561.

[2] C. Berell. Zur Kasuistik der Leukämie. Medical Times and Gazette, 284 (1868); Schmidt's Jahrbuch, 142, 167 (1869).

[3] E. Bohland und H. Schurz. Ueber die Harnsäure- und Stickstoffausscheidung bei Leukämie. Pflüger's Archiv, 47, 469 (1890).

[4] K. Hoffmann. Harnbeschaffenheit bei Leukämie lienalis. Wien. med. Wochenschrift, 20, 1036 (1870).

[5] R. Fleischer und F. Penzoldt. Klinische, pathologische, anatomische, und chemische Beiträge zur Lehre von der lienalen-, myologenen-, sowie der lymphatischen Form der Leukämie. Deutsche Arch. für klin. Medizin, 26, 368 (1880).

[6] G. Sticker. Beiträge zur Pathologie und Therapie der Leukämie. Zeitschr. für klin. Medizin, 14, 80 (1888).

[7] Ebstein. Ueber die acute Leukämie, u. s. w. Archiv. für klin. Med., 44, 343.

[8] Magnus-Levy. Ueber den Stoffwechsel bei acuter und chronischer Leukämie. Virchow's Archiv, 152, 107 (1898).

[9] G. Zagari e D. Pace. La genesi dell' acido urico e la gotta in riguardo alla patogenesi e all' indirizzo terapeutico. Napoli (1897). Centralblatt für innere Medizin, 19, 816 (1898).

[10] F. Galdi. Ueber die Alloxurkörper im Stoffwechsel bei Leukämie. Arch. für exp. Path. u. Pharmak., 49, 213 (1903).

[11] Parkes. The Composition of Urine. London, 331 (1860).

[12] H. Jacubasch. Beiträge zur Harnanalyse bei lienaler Leukämie. Virchow's Archiv, 43, 196 (1868).

[13] E. Reichardt. Blut und Harn bei Leukämie. Jenaische Zeitung f. Medizin und Naturwissenschaften, 5, 389 (1870).

[14] F. Schmuziger. Beiträge zur Kenntniss der Leukämie. Arch. d. Heilkunde, 17, 273 (1876).

[15] Bondzynski und Gottlieb. Ueber Xanthinkörper im Harn des Leukämikers. Arch. für exp. Path. u. Pharmak., 36, 127 (1895).

[16] R. Kolisch und H. Dostal. Das Verhalten der Alloxurkörper in pathologischen Harnen. Wien klin. Wochenschrift, 8, 413, und 435 (1895).

[17] P. Giacosa. Ueber die Bildung der Harnsäure im Organismus. Acadamie der Medicin, Turin, 1890, 6 Juni. Maly's Jahresb. über die Fortschritte der Thierchemie, 21, 182 (1891).

[18] J. Horbaczewski. Untersuchungen über die Entstehung der Harnsäure im Säugethierorganismus. Monatshefte für Chemie, 10, 624 (1889).

Ibid. Beiträge zur Kenntniss der Bildung der Harnsäure und der Xanthinbasen sowie der Entstehung der Leukocytose im Säugethierorganismus. Monatshefte für Chemie, 12, 221 (1891).

Spitzer [1] and Wiener [2] who confirmed the discovery of Giacosa and Horbaczewski, and who found also that the process is a vital one which ceases with the death of the cells of the spleen, and of Schittenhelm,[3] who prepared the active enzyme, has already been spoken of.

The apparent relation between the spleen and the formation of uric acid has led many authors to believe that uric acid is formed in the spleen. Neumeister [4] and Hammarsten [5] do not say precisely in their textbooks that the spleen does form uric acid, but that there is a very close relationship between the spleen and the formation of uric acid.

Other authors have maintained that the relation between the spleen and the formation of uric acid is not so very close. Thus, Mosler and Körner [6] found an increased excretion of uric acid in leukemia only when fever was present. Bartels [7] noted that splenic tumors sometimes occur without giving rise to an increased excretion of uric acid. According to Stadthagen,[8] certain pathological enlargements of the spleen, for example, pseudoleukemia, occur without any increased excretion of uric acid. In the case of a patient who had a steadily growing tumor of the spleen, Sticker [9] found that the quantity of uric acid in the urine varied without any relation to the growth of the tumor. Matthes [10] found the excretion of uric acid normal in leukemia,

[1] W. Spitzer. Die Uberführung von Nukleinbasen in Harnsäure durch die Säuerstoffübertragende Wirkung von Gewebsauszügen. Pflüger's Archiv, 76, 192 (1899).

[2] H. Wiener. Ueber Zersetzung und Neubildung der Harnsäure im thierischen Körper. Verhandl. des 17t Kongr. für innere Med., 622 (1899); also

Ibid. Ueber Zersetzung und Bildung der Harnsäure im Tierkörper. Arch. für exp. Path. u. Pharmak., 42, 375 (1900).

[3] A. Schittenhelm. Ueber die Harnsäurebildung im Gewebsauszügen. Zeitschr. für physiol. Chem., 42, 251 (1904), and

Ibid. Ueber die Fermente des Nukleinstoffwechsels. Zeitschr. für physiol. Chem., 43, 228 (1904).

[4] Neumeister. Lehrbuch der physiologischen Chem., 512 (1897).

[5] Hammarsten. Text Book of Physiological Chemistry (1898).

[6] F. Mosler und W. Körner. Zur Blut und Harnanalyse bei Leukämie. Virchow's Archiv, 25, 142 (1862).

F. Mosler. Zur Diagnose der lienalen Leukämie und der chemischen Beschaffenheit der Transudate und Sekrete. Virchow's Archiv, 37, 43 (1866).

[7] Bartels. Untersuchungen über die Ursache einer gestiegerten Harnsäureausscheidung in Krankheiten. Deutsch. Arch. für klin. Medizin, 1, 13 (1865).

[8] M. Stadthagen. Ueber das Vorkommen von Harnsäure in verschiedenen thierischen Organen, ihr Verhalten bei Leukämie und die Frage ihrer Entstehung aus den Stickstoffbasen. Virchow's Archiv, 109, 390 (1887).

[9] G. Sticker. Beiträge zur Pathologie und Therapie der Leukämie. Zeitschr. für klin. Medizin, 14, 80 (1888).

[10] M. Matthes. Zur Chemie des leukämischen Blutes. Berl. klin. Wochenschrift, 31, 531 (1894).

and Stuve,[1] Gumprecht,[2] and Magnus-Levy[3] found that only the normal amount of uric acid is excreted in chronic leukemia. Increased excretion of uric acid is not, therefore, a constant symptom of leukemia.

Mendel and Jackson[4] found that splenectomy does not affect the excretion of uric acid in dogs and cats when nuclein is administered or when it is not. Lo Monaco[5] observed no decrease in the excretion of uric acid in the case of a woman whose spleen had been extirpated. The evidence, then, does not indicate definitely that uric acid is formed in the spleen. At any rate, the spleen is not the only organ in which uric acid is formed.

CARTILAGE, CELLS OF THE DIGESTIVE TRACT, DIGESTIVE GLANDS, AND MUSCLES

It may be mentioned that Bartels[6] believed that uric acid is formed in the cartilage of the joints. According to this author the blood supply is poor in the joints and correspondingly the oxidation processes defective. Therefore, uric acid is formed. This idea is, of course, based on the old view that uric acid is a product of incomplete oxidation of proteid.

The work of Mares,[7] later confirmed by Kam,[8] who found the quantity of uric acid in the urine at different periods of the day parallel with the activity of the digestive glands is worthy of mention. Mares concluded that the uric acid is formed by the activity of the cells of the digestive glands from the material forming the cells.

The discovery of purin bodies in the feces during starvation by

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[1] R. Stuve. Beobachtungen über einem Fall von lymphatischen Leukämie. Festschr. des städt Krankenhauses zu Frankfurt a. M. (1896).

[2] Gumprecht. Alloxurkörper und Leukocyten beim Leukämiker. Centralbl. für allgem. Path. und pathol. Anat., 7, 820 (1896).

[3] A. Magnus-Levy. Ueber den Stoffwechsel bei acuter und chronischer Leukämie. Virchow's Archiv, 152, 107 (1898).

[4] L. Mendel and H. Jackson. On Uric Acid Formation after Splenectomy. Am. Journ. of Physiol., 4, 163 (1900).

[5] D. Lo Monaco. Osservazioni sull' escrezione e sulla formazione dell' acido urico nell' organismo. Bolletino della societa Lancisiani degli ospedali di Roma. 14. (2), 102 (1894), and Schmidt's Jahrbuch., 252, 109 (1896).

[6] Bartels. Untersuchungen über die Ursache einer gesteigerten Harnsäureausschei dung in Krankheiten. Deutsche Arch. für klin. Medizin, 1, 13 (1865).

[7] F. Mares. Sur l'origine de l'acide urique chez l'homme. Archives slaves de Biologie, 3 207 (1888); Centralbl. für die med. Wissen., 25, 2 (1898); Maly's Jahresb. über die Fortscritte der Thierchemie, 18, 112 (1888).

[8] B. Kam. Bijdragen tot de kennis der urinezuuruitscheidung. Dissert. Leiden (1898). Maly's Jahresb. über die Fortschritte der Thierchemie, 28, 573 (1898).

Weintraud[1] led him, and later Brandeburg[2] who confirmed Weintraud's discovery, to believe that at least a part of the uric acid excreted is formed by or from the mucous membrane of the alimentary canal. The discovery of purin bodies in the feces during starvation, in which case they cannot come from the food, has been confirmed by Petrén,[3] Krüger and Schittenhelm,[4] and Galdi.[5] Petrén[6] has likewise found purin bodies in feces free from bile. This work, however, does not give us any definite indication that uric acid is formed by any of the cells of the digestive tract.

The view first expressed by Siven[7] that uric acid is formed by muscular activity will also be remembered. His view is based only on his discovery that the excretion of uric acid is slightly increased by muscular work. In view of the work of Burian,[8] we must believe that muscular activity may be an important source of the endogenous uric acid.

THE LIVER

According to Cloetta,[9] Stokvis,[10] and Abeles,[11] uric acid is found in the liver of men, swine, the ox, and the horse. These authors,

[1] W. Weintraud. Zur Entstehung der Harnsäure im Saugethierorganismus. Verhandl. des 14t Kongr. für innere Med. (1896), 190, Wiesbaden, and Wien klin. Rundschau, 2 (1896); also

Ibid. Beiträge zum Stoffwechsel der Gicht. Charité Annalen, 275 (1895), also

Ibid. Ueber Harnsäurebildung beim Menschen. Vortrag geh. in der physiol. Gesell. zu Berlin am Marz (1895), and Du Bois Arch., 382 (1895).

[2] C. Brandeburg. Ueber die diagnostische Bedeutung der Harnsäure und Xanthinbasen in Urin. Berl. klin. Wochenschrift, 33, 137 (1896).

[3] K. Petrén. Ueber das Vorkommen, die Menge, und die Abstammung der Xanthinbasen in den Fäces. Skandinav. Arch. f. Physiol., 8, 315 (1898).

[4] M. Krüger und A. Schittenhelm. Die Purinkörper der menschlichen Fæces. Zeitschr. für physiol. Chem., 35, 153 (1902).

[5] F. Galdi. Ueber die Alloxurkörper im Stoffwechsel bei Leukämie. Arch. für exp. Path. u. Pharmak., 49, 213 (1903).

[6] K. Petrén. Nachtrag zur Mittheilung über das Vorkommen der Xanthinbasen in den Fäces. Skandinav. Arch. f. Physiol., 9, 412 (1899).

[7] V. Siven. Zur Kenntnis der Harnsäurebildung im menschlichen Organismus unter physiologischen und pathologischen Verhältnissen. Skandinav. Arch. f. Physiol., 11, 123 (1901).

[8] R. Burian. Die Bildung der Harnsäure im Organismus des Menschen. Med. Klin., 1, 131 (1905), and

Ibid. Die Herkunft der endogenen Harnpurin bei Mensch und Säugethiere. Zeitschr. für physiol. Chem., 43, 532 (1905).

[9] A. Cloetta. Ueber das Vorkommen von Inosit, Harnsäure, etc., im thierischen Körper. Ann. der Chem. u. Pharm., 99, 289 (1856).

[10] B. Stokvis. Bijdragen tot de physiologie van het acidum uricum. Ned. Tijdschr. IV, p. 587, Afl., Oct., 1859. Arch. f. d. holl. Beitr., p. 260 (1860), und Schmidt's Jahrb., 109, 4 (1861).

[11] M. Abeles. Ueber Harnsäure im Blute und einigen Organen und Geweben. Wien. med. Jahrb., 83, 479 (1887), and Jahresb. über die Fortschritte der ges. Med., 1, 120 (1887).

however, found uric acid in several other organs. The discovery cannot be considered to indicate that uric acid is formed in the liver.

Salomon [1] and Horbaczewski [2] have found that uric acid is formed by the autodigestion of ox liver after slight decomposition. Salkowski,[3] Spitzer,[4] and Wiener [5] found that this is a vital process which ceases when the cells are killed. These authors found also that other organs, for example, spleen, thymus, pancreas, give uric acid in the same way. Wiener found further that the liver can oxidize hypoxanthin to uric acid. The liver of the dog does not act like the horse, ox, and swine liver in this respect.[5]

Sticker,[6] Horbaczewski,[7] and Mendel and Jackson [8] found that the excretion of uric acid is increased in cirrhosis of the liver in man. Hahn and Nencki,[9] Nencki, Pawlow, and Zalesky,[10] and De Filippi [11] found increased excretion of uric acid after partial exclusion of the liver of dogs from the circulation by Eck's fistula. Lieblein [12] found increased excretion of uric acid in dogs after artificial degeneration of hepatic tissue of dogs from injections of acid into the bile duct, and Horbaczewski [7] after degeneration of human liver from phosphorus poisoning. Münzer,[13] too, found no

[1] G. Salomon. Zur Physiologie der Xanthinkörper. Arch. für Physiol., 361 (1881).

[2] J. Horbaczewski. Beiträge zur Kenntniss der Bildung der Harnsäure und der Xanthinbasen, sowie der Entstehung der Leukocytose im Säugethierorganismus. Monatshefte für Chemie, 12, 221 (1891).

[3] E. Salkowski. Ueber Autodigestion der Organe. Zeitschr. für klin. Medizin, 17 Suppl., 77 (1890).

[4] Spitzer. Die Uberführung von Nukleinbasen in Harnsäure durch die Sauerstoffübertragende Wirkung von Gewebsauszügen. Pflüger's Archiv, 76, 192 (1899).

[5] H. Wiener. Ueber Zersetzung und Bildung der Harnsäure im Tierkörper. Arch. für exp. Path. u. Pharmak., 42, 375 (1899), also

Ibid. Ueber Zersetzung und Neubildung der Harnsäure im thierischen Körper. Verhandl. des 17t Kongr. für innere Med., 622 (1899).

[6] G. Sticker. Beiträge zur Pathologie und Therapie der Leukämie. Zeitschr. für klin. Medizin, 14, 80 (1888).

[7] J. Horbaczewski. Untersuchungen über die Entstehung der Harnsäure im Säugethierorganismus. Monatshefte für Chemie, 10, 624 (1889).

[8] L. Mendel and H. Jackson. On Uric Acid Formation after Splenectomy. Am. Journ. of Physiol., 4, 163 (1900).

[9] Hahn und Nencki. Archives des sciences biologiques de St. Petersbourg, 1, 401 (1892).

[10] Nencki, Pawlow, und Zalesky. Ueber den Ammoniakgehalt des Blutes und der Organe und die Harnstoffbildung bei den Säugethieren. Arch. für exp. Path. u. Pharmak., 37, 49 (1896).

[11] F. De Filippi. Recherches sur l'echange material des chiens opérés de fistule d'Eck. Archives italiennes de biologie, 31, 211 (1899), and

Jahresber. über die Leistungen und Fortschritte in der Gesammten Medicin (1899).

[12] V. Lieblein. Die Stickstoffausscheidung nach Leberveröderung beim Saugethiere. Arch. für exp. Path. u. Pharmak., 33, 318 (1894).

[13] E. Münzer. Der Stoffwechsel bei akuter Phosphorvergiftung. Deutsche Arch. für klin. Medizin, 52, 199 (1891).

decreased excretion of uric acid after degeneration of human liver from phosphorus poisoning. On account of these facts, Horbaczewski,[1] Mendel and Jackson,[2] and others think that uric acid cannot be formed in the liver, that if the liver forms uric acid, we should expect a decreased excretion of uric acid rather than an increased excretion when the functions of the liver are interfered with.

As we shall see later, we have fairly satisfactory evidence that uric acid is destroyed by the liver in dogs. It is probable, therefore, that in dogs, at any rate, Neumeister's explanation[3] is correct. This author believes that the increased excretion of uric acid after Eck's fistula is due to the fact that uric acid is normally destroyed by the liver, and that when the liver is cut out of the circulation, a larger quantity of uric acid than usual escapes oxidation. In the case of man, the increased excretion of uric acid in cirrhosis of the liver may be due to oxidation of purin bases from the nucleoproteid of the nuclei of the degenerated cells, as suggested by Pick[4] in the case of dogs after injection of acid into the bile duct. We have, then, no positive indication that uric acid is not formed in the liver.

Wiener[5] found that uric acid is formed by the autolysis of the liver, thymus, and spleen of the ox. Less uric acid is obtained from the spleen and thymus than from the liver. If chopped-up spleen or thymus be added to the liver, more uric acid is obtained than from either organ alone. Further, if an alcoholic extract of the thymus or spleen, which is free from purin bodies, be added to the liver, more uric acid is obtained than from the liver alone. Wiener explains his work by assuming that there is some compound in the thymus and spleen soluble in alcohol, from which uric acid can be formed synthetically by the action of the liver. It is possible that the alcoholic extract of thymus and spleen contains something that increases the rate at which uric acid is formed from the purin bases of the cell nuclei of the liver. This would explain Wiener's results, for he determined only the amount

[1] J. Horbaczewski. Beiträge zur Kenntniss der Bildung der Harnsäure und der Xanthinbasen, sowie der Entstehung der Leukocytose im Säugethierorganismus. Monatshefte für Chemie, 12, 221 (1891).

[2] L. Mendel and H. Jackson. On Uric Acid Formation after Splenectomy. Am. Journ. of Physiol., 4, 163 (1900).

[3] Neumeister. Lehrbuch der physiologische Chemie, 1st ed., part 2, p. 236.

[4] E. Pick. Versuche über functionelle Ausschaltung der Leber bei Säugethieren. Arch. für exp. Path. u. Pharmak., 32, 382 (1893).

[5] H. Wiener. Ueber synthetische Bildung der Harnsäure im Thierkörper. Verhandl. des 19t Kongr. innere Med., 383 (1901), and Hofmeister's Beiträge, 2, 42 (1902),

of uric acid formed in four hours. Or, it may be that the liver normally oxidizes as well as forms uric acid, and that the addition of the alcoholic extract of spleen and thymus partially inhibits the process by which uric acid is destroyed.

It will be remembered that Wiener found that uric acid can be synthesized in birds from urea and certain dibasic acids of the aliphatic series and compounds allied to them. There are three of these, namely, tartronic acid, glycerin, and dialuric acid, which, when added to chopped-up ox liver undergoing autolysis, cause the formation of a larger quantity of uric acid than is formed by simple autolysis of the liver itself. According to Wiener, uric acid is synthesized from these three compounds by the liver. We have already seen Burian's explanation of Wiener's results showing that dialuric and tartronic acids merely increase the rate of the reaction by which uric acid is formed from the purin bodies of the nucleoproteids of the liver cells.

Summary

At the present time we believe that the uric acid in the urine comes from two sources, — the purin bases in food and those in the body. These purin bases in turn come from the nucleoproteids of the cell nuclei. Concerning the exogenous nucleoproteids, all we can say is that nucleins can be split off from nucleoproteids by the action of pepsin hydrochloric acid, and that this action may, therefore, take place in the stomach. The autolytic experiments on different organs seem to indicate that most of those organs containing large amounts of nucleoproteids can form uric acid. This, of course, is endogenous uric acid. It is possible that there is no special organ in which any of the changes from nucleoproteid to uric acid take place. At any rate, we know that several enzymes which bring about the successive changes from nucleoproteid to uric acid are found in many organs of the body, and it has been suggested by Wiener that other organs, as, for example, the liver of the dog, which does not seem to form uric acid, have this power, but have also the power of oxidizing uric acid when once formed. We must also bear in mind the work of Burian [1] on the formation of uric acid by active muscles.

[1] R. Burian. Die Bildung der Harnsäure im Organismus des Menschen. Med. Klinik, 1, 131 (1905).

Die Herkunft der endogenen Harnpurine bei Mensch und Säugethiere. Zeitschr. für physiol. Chem., 43, 532 (1905).

Organ of Decomposition of Uric Acid

IN CARNIVORA

Stokvis [1] was the first to observe that a dog's liver undergoing autolysis has the power of destroying uric acid. His discovery has since been confirmed by Wiener [2] and Jacoby.[3] These authors added uric acid to finely divided liver and to the aqueous extract of liver and found that the uric acid became destroyed in a day or so if the mixture were left in a warm place.

After Richet [4] and Gottlieb [5] found that urea is formed during the autolysis of dog liver, Chassevant and Richet [6] found that if sodium urate be added to the liver, it gradually disappears during the process of autolysis, and that the urea increases. Richet [7] later found that the alcoholic precipitate of the aqueous extract of liver, containing probably purin bodies, also causes an increase in the urea when added to a liver undergoing autolysis. These authors did not state the method used for the determination of urea.

Ascoli [8] obtained a similar result by another procedure. This author found that if defibrinated ox blood containing uric acid be circulated artificially through a freshly extirpated dog liver, the uric acid gradually disappears and urea appears. Ascoli used the Schöndorff [9] method for the determination of urea.

Spitzer [10] repeated the work of Chassevant and Richet, but could not find that the amount of urea present in the autodigestion exper-

[1] B. Stokvis. Bijdragen tot de physiologie van het acidum uricum. Ned. Tijdschr., 3, p. 587, Afl., Oct. (1859); Arch. f. d. holl. Beitr., p. 260 (1860), und Schmidt's Jahrb., 109, 4 (1861).

[2] H. Wiener. Zersetzung und Neubildung der Harnsäure im thierischen Körper. Verhandl. des 17 Kongr. f. innere Med., 622 (1889), also

Ibid. Ueber Zersetzung und Bildung der Harnsäure im Tierkörper. Arch. für exp. Path. u. Pharmak., 42, 375 (1899).

[3] M. Jacoby. Ueber die Oxydationsfermente der Leber. Virchow's Archiv, 157, 235 (1899).

[4] C. Richet. De la formation d'urée dans le foie après la mort. Comptes rendus, 118, 1125 (1893).

[5] Gottlieb. Ueber Xanthinkörper im Harn. München med. Wochenschrift, 42, 788 (1895).

[6] Chassevant et Richet. Des ferments solubles uropoiétiques du foie. Comptes rendus de la société de biologie, 10 ser., 4, 743 (1897).

[7] Richet. Comptes rendus de la société de biologie, 368 et 525 (1894).

[8] G. Ascoli. Ueber die Stellung der Leber im Nucleinstoffwechsel. Pflüger's Archiv, 72, 340 (1898).

[9] B. Schöndorff. Eine Methode der Harnstoffbestimmung in thierischen Organen und Flussigkeiten. Pflüger's Archiv, 62, 34 (1896).

[10] W. Spitzer. Weitere Beobachtungen über die oxydativen Leistungen thierischer Gewebe. Pflüger's Archiv, 71, 596 (1898).

iments is increased by addition of uric acid or urate. Loewi [1] repeated this work carefully and found that no urea is formed from uric acid in the autolysis experiments. Loewi used the nitric acid test for urea. He found that a nitrogenous body, which he described, is formed from the uric acid, and he thinks it is an amido acid. Jacoby [2] and Burian and Schur [3] believe that, according to the description, the body called an amido acid by Loewi is really allantoin. This seems very probable when we remember that uric acid is oxidized to allantoin in dogs. Further, the properties of allantoin and urea are similar in many points, so that the " urea " of Chassevant and Richet might well have been allantoin. In Schöndorff's method of determination, urea, allantoin, and alloxantin are all determined as urea, so that in the experiments of Ascoli, who used this method, allantoin was probably called urea. At any rate, some nitrogenous body is formed from the uric acid in these autolysis experiments and it is not urea. The objection, therefore, that we have only an apparent disappearance of uric acid due to the fact that the determination of uric acid is affected by the presence of some of the products of autolysis is not valid.

It will be remembered that Stadeler,[4] Nencki and Sieber,[5] and Kreidl [6] found that uric acid in alkaline solution is oxidized by the oxygen of the air to uroxanic acid. This might be taken as explanation of the disappearance of uric acid in the autolysis experiments. None of those who performed these experiments on the dog liver took the precaution to do control experiments after killing the liver by boiling. This should be done, for it is not known if uroxanic acid could be mistaken for urea in the Schöndorff method for determining urea. Wiener performed control experiments in this way on the kidney of the ox, which destroys uric acid, and obtained negative results. It is probable,

[1] O. Loewi. Ueber das harnstoffbildende Ferment der Leber. Zeitschr. für physiol. Chem., 25, 511 (1898).

[2] M. Jacoby. Ueber die Oxydationsferments der Leber. Virchow's Archiv, 157, 235 (1899).

[3] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. 2. Mitth. Pflüger's Archiv, 87, 239 (1901).

[4] G. Stadeler. Ueber die Uroxansäure, ein Zersetzungsprodukt der Harnsäure. Ann. d. Chem. u. Pharm., 78, 286 (1851).

[5] M. Nencki und N. Sieber. Ueber die Zersetzung des Traubenzucker und der Harnsäure durch Alkalien bei der Bluttemperatur. Journ. für prakt. Chem. (2), 25, 498 (1881).

[6] I. Kreidl. Bestimmungsmethode für Harnsäure und Beobachtungen an Harnsäurelösungen. Monatshefte für Chemie, 14, 109 (1893).

therefore, that, in the dog liver, the oxidation process is a vital one. Further, after he confirmed the work showing that the dog liver destroys uric acid, Wiener [1] showed that if dog liver extract be added to the liver extract of an ox, which latter forms uric acid from its own material, the uric acid formed is destroyed.[2] On standing, the amount of uric acid in the mixture of dog liver and ox liver diminishes. This seems to indicate that the destruction of uric acid by the dog liver is a vital process. Wiener found also that the dog kidney possesses, to a less extent than the liver, the power of destroying uric acid.

That the liver destroys uric acid in dogs and cats is indicated also by the work of Burian and Schur.[3] These authors found no uric acid in the blood after kidney extirpation even when thymus was fed, but did find it when the liver as well as the kidney is extirpated. The absence of the kidney prevents the uric acid from being excreted. The absence of the liver prevents it from being destroyed. When both organs are extirpated, the uric acid is neither destroyed nor excreted. It is stored up in the blood.

It will be remembered that Hahn, Massen, Nencki, and Pawlow [4] found that after Eck's fistula, there is an increase in the uric acid in the urine of dogs, and that Lieblein [5] and Pick [6] obtained the same result after liver necrosis caused by injecting acid into the bile duct. This has been taken as an indication that the liver is the organ in dogs which decomposes uric acid,[7] and that when the functions of the liver are interfered with, less uric acid is destroyed than normally. But, as we have seen, there is another explanation. The degeneration of the cell nuclei, observed by Pick,[6] would ac-

[1] H. Wiener. Ueber Zersetzung und Neubildung der Harnsäure im thierischen Körper. Verhandl. des 17t Kongr. für innere Med., 622 (1899), also

Ibid. Ueber Zersetzung und Bildung der Harnsäure im Tierkörper. Arch. für exp. Path. u. Pharmak., 42, 375 (1899).

[2] *Ibid.* Ueber synthetische Bildung der Harnsäure im Thierkörper. Hofmeister's Beiträge, 2, 42 (1902).

[3] H. Burian und R. Schur. Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. 2. Mitth. 87, 239 (1901).

[4] H. Hahn, O. Massen, M. Nencki, und J. Pawlow. Die Eck'sche Fistel zwischen der unteren Hohlvene und der Pfortader und ihre Folgen für der Organismus. Arch. für exp. Path. u. Pharmak., 32, 161 (1893).

[5] V. Lieblein. Die Stickstoffausscheidung nach Leberveröderung beim Säugethieren. Arch. für exp. Path. u. Pharmak., 33, 318 (1894).

[6] E. Pick. Versuche über functionelle Ausschaltung der Leber bei Säugethieren. Arch. für exp. Path. u. Pharmak., 32, 382 (1893).

[7] Neubauer. Physiologische Chemie.

count for this increased excretion of uric acid, so that we cannot use it as proof of the fact that that uric acid is destroyed by the liver in dogs. Yet Neubauer's explanation would account for the fact noticed by Hahn, Massen, Nencki, and Pawlow, that the excretion of uric acid is especially high on a meat diet after Eck's fistula, for we should expect less of the uric acid formed from the hypoxanthin of the meat extract to be destroyed than when the liver is present. It may be that Neubauer's explanation is the correct one in case of Eck's fistula, and Pick's explanation in the case of liver degeneration. A determination of the allantoin in the urine of dogs with Eck's fistula and after acid necrosis of hepatic tissue would probably show which theory is correct. According to Neubauer's theory, we should expect decreased allantoin; according to Pick, increased allantoin.

Pohl [1] found that there is no allantoin in the fresh organs of the dog, but that after undergoing autolysis for several hours, allantoin is formed by the mucous membrane of the alimentary canal, the liver, thymus, the spleen, and pancreas. The amount of allantoin increases with the time. Allantoin is not formed by the blood or muscle during autodigestion.

Croftan [2] has studied the decomposition of uric acid in dogs and cats. His method of procedure was as follows: The organs studied were desanguinated, ground up finely, and allowed to stand under alcohol. The alcohol was then filtered off and the residue washed with ether and allowed to dry in the air. This residue was finally extracted with water containing NaF. One gram of uric acid was suspended in 1,000 cc. of water and dissolved by addition of Na_2CO_3. About 100 cc. of this urate solution was added to the organ extract in each case. Three solutions, I, II, and III, were prepared in this way. In flask I the uric acid was determined immediately. The contents of flask II were heated to boiling and allowed to stand at 38° C. for forty-eight hours. The contents of flask III were not boiled, but were allowed to stand at 38° C. for forty-eight hours. The uric acid in flasks II and III was determined at the end of forty-eight hours. In flask II the boiling destroys the ferment.

[1] J. Pohl. Ueber Allantoinausscheidung bei Intoxicationen. Arch. für exp. Path. u. Pharmak., 48, 367 (1902).

[2] A. Croftan. Synopsis of experiments on the transformation of circulating uric acid in the organism of man and animals. Med. Record, 64, 6 (1903).

Flask II, then, acts as a check on flask III. The results are shown in the table.

		I	II	I—II	III	I—III	Per cent destroyed
Dog	liver	0.327	0.325	0.002	0.225	0.102	31.1
	kidney	0.319	0.319	0.000	0.312	0.007	2.4
	muscle	0.330	0.326	0.004	0.303	0.027	8.2
	blood	0.321	0.317	0.004	0.313	0.008	2.5
	spleen	0.327	0.320	0.007	0.319	0.008	2.4
Cat	liver	0.331	0.326	0.005	0.239	0.092	28.0
	kidney	0.327	0.326	0.001	0.318	0.009	2.6
	muscle	0.316	0.310	0.006	0.291	0.025	7.8
	blood	0.316	0.314	0.002	0.305	0.011	2.6
	spleen	0.332	0.328	0.004	0.326	0.006	1.9

It will be seen that the liver is the most active organ in the destruction of uric acid. The muscles also have some uric acid destroying power. Croftan has suggested that while weight for weight the liver is more active than muscles, the latter may be more important, physiologically, on account of their much greater bulk. The results in the case of the other organs do not seem to show much greater destruction than the check experiments.

Croftan went further and studied the ferment, which, he says, though he does not give the details of his work, consists of a nucleoproteid, an albumose which is powerless alone, and certain salts which hold the albumose in solution. He states that the albumose is probably the specific agent, for the nucleoproteid is found universally in those organs which do not destroy uric acid. The nucleoproteid has the power of dissociating H_2O_2 and giving out oxygen, and therefore probably acts as a carrier of oxygen in the process. He finds that certain salts, for example, nitrates and cyanates, diminish the power of the nucleoproteid to liberate oxygen. Other compounds, for example, alkalies and salicylates, greatly increase it. The author suggests that good effect of alkalies and salicylates in gout may be connected with this action.

IN OTHER MAMMALS

According to Stokvis,[1] if uric acid is added to horse liver undergoing autolysis, the uric acid is destroyed. The swine

[1] B. Stokvis. Bijdragen tot de physiologie van het acidum uricum. Ned. Tijdschr., 3, p. 587, Afl., Oct. (1859); Arch. f. d. holl. Beitr., 260 (1860), and Schmidt's Jahrb., 109, 4 (1861).

liver, also, according to Wiener [1] destroys uric acid when undergoing autolysis. Wiener [1] found, too, that the kidney of the horse and ox destroy uric acid, and that this is a vital process destroyed by boiling. Lang [2] and Schittenhelm [3] likewise found that the liver and kidney of the ox can destroy uric acid. Lang [2] found, too, that the spleen and intestinal wall can destroy uric acid.

Wiener,[1] Lang,[2] Schittenhelm,[3] and Burian [4] have shown that muscle is capable of destroying uric acid. Although the power of the ox muscle for destroying uric acid is less than that of the kidney, Wiener thinks that on account of the greater quantity of muscle in the body it may be of more importance in the oxidation of uric acid than the kidneys.

Ascoli [5] found that ox blood destroys uric acid during autolysis.

Cippolina [6] found more oxalic acid in the liver and spleen of the ox and calf after they had undergone autolysis for a few hours if uric acid had been previously added than if the uric acid were not added. He assumed that the uric acid is oxidized to oxalic acid, and therefore that the liver and spleen of the ox and calf are the organs in which the oxidation takes place. We have seen, however, that it is doubtful if oxalic acid is formed in the body as an oxidation product of uric acid. Further, it has been shown by Wiener that the uric acid content of the liver and spleen of the ox and calf increases during autolysis, that, therefore, these organs form uric acid. He has suggested, however, that both formation and destruction of uric acid may go on at the same time in the various organs, and that whether the increase in uric acid is positive or negative in any organ depends on whether the process of formation or process of destruction is more active. He has, in fact, shown that under certain conditions even the liver of the

[1] H. Wiener. Ueber Zersetzung und Neubildung der Harnsäure im thierischen Körper. Verhandl. des 17t Kongr. für innere Med., 622 (1899), also

Ibid. Ueber Zersetzung und Bildung der Harnsäure im Tierkörper. Arch. für exp. Path. u. Pharmak., 42, 375 (1899).

[2] S. Lang. Ueber desamidierung im Tierkörper. Hofmeister's Beiträge, 5, 321 (1904).

[3] A. Schittenhelm. Ueber die Fermente des Nukleïnstoffwechsels. Zeitschr. für physiol. Chem., 43, 228 (1904).

[4] R. Burian. Die Herkunft der endogenen Harnpurine bei Mensch und Säugethiere. Zeitschr. für physiol. Chem., 43, 532 (1905).

[5] G. Ascoli. Ueber die Stellung der Leber im Nukleinstoffwechsel. Pflüger's Archiv, 72, 340 (1898).

[6] Cippolina. Ueber die Oxalsäure im Organismus. Berl. klin. Wochenschrift, 38, 544 (1901).

dog can form uric acid, and Burian [1] has shown that the liver of the ox can destroy uric acid.

Croftan performed experiments with the organs of herbivora and omnivora, as well as those of dogs and cats. The method of experimenting b[illegible] explained a few pages back. The results are shown in the following table:

			I	II	I—II	III	I—III	Per cent destroyed
Herbivora	Cow	liver	0.331	0.327	0.004	0.322	0.009	2.7
		kidney	0.321	0.316	0.005	0.236	0.085	26.4
		muscle	0.327	0.321	0.006	0.305	0.022	6.8
		spleen	0.313	0.309	0.004	0.306	0.007	2.1
	Rabbit	liver	0.314	0.309	0.005	0.306	0.008	2.6
		kidney	0.316	0.314	0.002	0.239	0.077	24.3
		muscle	0.331	0.324	0.007	0.311	0.020	6.0
		blood	0.324	0.322	0.002	0.317	0.007	2.2
		spleen	0.321	0.317	0.004	0.314	0.007	2.2
Omnivora	Hog	liver	0.332	0.326	0.006	0.238	0.094	28.2
		kidney	0.326	0.321	0.005	0.247	0.079	24.2
		muscle	0.318	0.317	0.001	0.299	0.019	6.2
		spleen	0.331	0.324	0.007	0.325	0.008	2.4
	Man	liver	0.319	0.314	0.005	0.200	0.119	37.4
		kidney	0.327	0.325	0.002	0.188	0.139	42.6
		muscle	0.322	0.319	0.003	0.299	0.023	7.2
		spleen	0.332	0.324	0.006	0.325	0.007	2.2
		blood	0.326	0.320	0.006	0.318	0.008	2.6

It will be seen that while in carnivora the liver is the most active organ, in herbivora the kidneys are the most active. In omnivora both the liver and the kidneys are active in destroying uric acid. In all cases the muscles are active to about the same extent.

Wiener [2] has stated that he obtained the uric acid destroying ferment free from cells. His experiments are not yet concluded, however.

Summary

Our knowledge concerning the destruction of uric acid in the body depends chiefly on observations on the autolytic action of isolated organs. While it is not absolutely correct to draw from

[1] R. Burian. Ueber die Oxydative und die vermeintliche synthetische Bildung von Harnsäure in Rinderleberauszug. Zeitschr. für physiol. Chem., 43, 497 (1905).

[2] H. Wiener. Ueber Harnsäurezersetzung durch Organferment. Centralblatt für Physiol., 18, 690 (1904).

these experiments alone conclusions concerning the action of the organs when they form a part of the living organ, yet it seems probable that uric acid is destroyed by the liver in carnivora, and to a lesser extent by the muscles, and perhaps also by the thymus, spleen, pancreas, and kidney, by the kidneys in herbivora, and by both the kidneys and liver in omnivora.

The Effect of Drugs on the Metabolism of Uric Acid

In speaking of the therapeutics in gout, Minkowski [1] says " that whatever may be the interpretation of the pathological processes in different instances, the aims of therapeutics may be divided into three classes:

" 1. Treating the primary defects in the metabolism.

" 2. Influencing especially the metabolism of the uric acid.

" 3. Treating the individual symptoms in different cases."

This evidently covers the field of therapeutics in gout.

As we shall see later, we do not know at present in what way the metabolism in gout is abnormal. So far, then, scientific medicine has nothing to offer in the way of a direct treatment of the fundamental disturbances in the metabolism of gout. Clinical observation has shown the deleterious influence of high living, abuse of alcohol, lack of exercise, and lead poisoning, and the good effect of certain drugs, frugal living, exercise, massage, and bathing on gout. There are, therefore, indirect methods of treatment of the first class, but as these methods belong to the field of clinical medicine, they will not be considered here. The methods of treating the individual symptoms in different cases of gout belong also to the field of clinical medicine.

In regard to influencing the metabolism of uric acid, Minkowski says that we should " endeavor to prevent the body from becoming highly charged with uric acid." He gives four methods of doing this, viz.:

(*a*) By decreasing the formation of uric acid.

(*b*) By furthering the excretion.

(*c*) By hastening the further oxidation.

(*d*) By increasing the solubility of the uric acid in the blood and tissues.

[1] More or less literal from Minkowski. Die Gicht, p. 271. Specielle Pathologie und Therapie von H. Nothnagel, Bd. 7, Th. 3 (1903).

There is some doubt whether, in treating gout, there is any value in bringing about these results spoken of by Minkowski. This point will be taken up later in the section on gout. But in this chapter we shall see how we can bring about the result stated under (*a*), (*b*), (*c*), and (*d*) by drugs, for it is very generally considered that we should try to have as little uric acid formed as possible in gouty people, and to rid the organism of it as rapidly as possible. Ebstein[1] has, in fact, defined the uric acid diathesis as "a pathological disposition of man in consequence of which, without known functional or organic primary disturbance, more uric acid is formed than normally."

Under the head of the so-called uric acid diathesis there is another abnormal tendency, that of forming uric acid calculi and gravel. In speaking of the treatment of this tendency, von Noorden[2] says that we should (1) give large quantities of water to increase the dissolving power of the urine for uric acid; (2) give such food as gives rise to little uric acid; (3) administer drugs which, after passing through the body, make the urine a better solvent for uric acid; (4) keep out of the food substances which, after passing through the body, make the urine a poor solvent for uric acid.

The value and the uselessness of these various methods of influencing the metabolism of uric acid will be discussed later. We have already seen the effects of different kinds of foodstuffs on the formation of uric acid. There remains to be considered the effect of drugs and large quantities of water on the dissolving power of the urine and blood for uric acid, and of the effect of drugs on the formation of uric acid.

The Effect of Drugs on the Solubility of Uric Acid in the Urine

In cases of uric acid stones and gravel, one of the chief aims of therapeutics has been to make the urine a better solvent for uric acid. The patient is sometimes recommended to drink large quantities of water. In cases in which only a slight precipitation of uric acid occurs in the warm urine, we might succeed in holding a larger quantity of uric acid in solution by greatly increased diuresis, but in a solution of uric acid so highly saturated as

[1] Ebstein. Die Natur und Behandlung der Harnsteine. Wiesbaden, 1884.

[2] C. v. Noorden. Zur Behandlung der harnsäuren Nierenconcremente. Verhandl. des 14t Kongr. für innere Med. (1896).

urine, we should scarcely expect to dissolve much of the gravel already formed by increased diuresis, especially since the gravel and stones are usually somewhat protected from solution by the organic material which covers them. Large quantities of urine would probably act as a good mechanical agent in washing out gravel.

The alkalies have always been highly recommended in the treatment of uric acid calculi. The theory has been that since the salts of uric acid are more soluble than uric acid itself, alkalies, or compounds which change to alkalies on passing through the body, would make the urine less acid, and would also give uric acid as a soluble salt rather than the insoluble free acid. In treating the subject of uric acid in the urine, we have already seen how this view must be considerably modified. The conclusions arrived at in that part of the book were that determinations of the acidity of the urine by titration methods were entirely unreliable, that facts concerning the behavior of cold urine do not apply to urine at the body temperature, that the action of alkalies on a normal urine at the body temperature is different from the action of alkalies on a urine from which the gravel deposits at 37°, and finally that the administration of alkalies in quantities insufficient to make the urine almost alkaline cannot affect the solubility of uric acid.

Tunicliffe and Rosenheim [1] found that certain of the organic bases — and inorganic bases would undoubtedly have acted in the same way — made normal urine at the body temperature a much better solvent for uric acid than the urine itself. As we have already seen, however, urine from which uric acid deposits at the body temperature corresponds in this respect at the body temperature to normal urine at the room temperature, and therefore alkalies, unless added in quantities sufficient to decrease very considerably the acidity as determined by titration, can have little effect on the dissolving power of the urine for uric acid. When alkali enough is given to make the urine almost alkaline at the body temperature, we should expect that even a urine which deposits uric acid would be a better solvent than it ordinarily is in uric acid. It is doubtful if a nearly saturated solution of uric acid, such as urine, even when it is nearly alkaline,

[1] F. Tunicliffe and D. Rosenheim. Piperidine as a Uric Acid Solvent, a comparative study. Lancet (1898), 2, 198.

will have much effect on uric acid which is once precipitated, especially since the crystals are somewhat protected by a covering of mucous-like organic material.

The inorganic alkalies, the carbonates of lithium, sodium, and potassium, the bicarbonate of sodium, and $CaH_2(CO_3)_4$ and mineral waters containing these bodies have been used longest as uric acid solvents. Pfeiffer [1] found after use of $LiCO_3$, Na_2CO_3, or the alkaline Carlsbad Muhlbrunnen water, that less uric acid is given up to the uric acid filter than before using the water. This is what we should expect. According to our explanation of the behavior of uric acid in the urine, and of Pfeiffer's results, the addition of alkali should influence the equilibrium between uric acid and the other acid bodies in the urine in such a direction that less uric acid is precipitated on the uric acid filter than before adding the alkali. But we cannot conclude from Pfeiffer's results that in a urine which tends to deposit gravel we can prevent the deposition by administration of alkaline waters. Pfeiffer [2] found later that Fachinger water which contains $CaH_2(CO_3)_4$ acts like the other alkalies in this respect. As we should expect from theoretical considerations, Pfeiffer [1] found that water containing chiefly only NaCl (Wiesbadener Kochbrunner) has no influence on the dissolving power of the urine for uric acid. The decrease of the "free" uric acid by Na_2CO_3 has been confirmed by Neumayer.[3]

$CaCO_3$ and $CaH_2(CO_3)_4$ have also been recommended by v. Noorden [4] and others because of their belief that these compounds increase the ratio *alkaline sodium phosphate* : *acid sodium phosphate*. Ritter [5] had shown that a high value for this ratio has a favorable influence on the solvent power of the urine for uric acid.

Rosenfeld [6] could not find that alkalies have any influence on the solvent power of the urine for uric acid.

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[1] E. Pfeiffer. Zur Aetiologie und Therapie der Gicht. Verhandl. des 5t Kongr. für innere Med., 444 (1886).

[2] *Ibid.* Zur Behandlung verscheidener Nierenkrankungen. Berl. klin. Wochenschrift, 27, 445 (1890), and

Ibid. Ueber Harnsäure und Gicht. Berl. klin. Wochenschrift, 29, 383, 412, 461, 490, und 536 (1892).

[3] H. Neumayer. Discussion in d. Versamml. des 14t Kongr. für innere Med., 424 (1896).

[4] v. Noorden. Zur Behandlung der harnsäuren Nierenconcremente. Verhandl. des 14t Kongr. für innere Med. (1896).

[5] A. Ritter. Ueber die Bedingungen für die Entstehung harnsäurer Sedimente, ein Beitrag zur Theorie der Gicht. Zeitschr. für Biol., 35, 155 (1897).

[6] G. Rosenfeld. Grundzüge der Behandlung der harnsäuren Diathese. Verhandl. des 14t Kongr. für innere Med., 318 (1896).

The experiments of Schreiber and Zaudy [1] indicate that alkalies very slightly increase the solubility of the uric acid in the urine. Meisls [2] added Li CO_3 to a urine and found that the solvent power of the urine for uric acid is not increased. Ortowski [3] tested carefully the action of addition of $NaHCO_3$ to urine on its power of dissolving uric acid, and found that there is no effect. The inorganic alkalies, then, seem to have little effect on the solubility of uric acid in cold urine.

The organic bases, piperazin, lysidin, piperidine, lycetol, have been introduced as therapeutic agents in uric acid gravel and stones on account of the fact that the urates of these bases are even more soluble than the urates of the inorganic alkalies.[4]

Biesenthal and Schmidt [5] and Majert and Schmidt [6] found that a dilute aqueous solution of piperazin dissolves uric acid in large amounts. Biesenthal and Schmidt [7] therefore recommended piperazin in cases of uric acid calculi, and stated that they obtained good clinical results from it in such cases.

Mendelsohn [8] and Meisls [2] confirmed the observations showing

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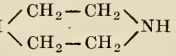
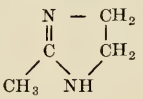
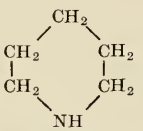
[1] Schreiber und Zaudy. Zur Wirkungen der Offenbacher Kaiser Friedrichs-Quelle. Zeitschr. für diät- und physikal. Therapie, 2, 136 (1899).

[2] W. Meisls. Experimente mit Piperazin und anderen uratlösenden Mitteln. Ungarisches Arch. für Med., 1, 364 (1893). Maly's Jahresb. über die Fortschritte der Thierchemie, 23, 582 (1893).

[3] W. Ortowski. Vergleichende Untersuchungen über Urotropin, Piperazin, Lysidin, Uricedin, und Natron bicarbonicum bei der harnsäuren Diathese. Zeitschr. für klin. Med., 40, 331 (1900).

[4] Piperazin is diethylendiamin 

Lysidin is ethylenethylenyldiamin, 

Piperidine is  lycetol is dimethylpiperazin (dipropylendiamin).

[5] Biesenthal und Schmidt. Piperazin bei Gicht und Steinleiden. Berl. klin. Wochenschrift, 28, 1214, and 1231 (1891).

[6] W. Majert und A. Schmidt. Ueber das Piperazin. Ber. der Dtsch. chem. Gesell., 23, 3722 (1890).

[7] Biesenthal und Schmidt. Klinisches über das Piperazin. Berl. klin. Wochenschrift, 29, 28 (1892).

[8] M. Mendelsohn. Uber Harnsäurelösung, insbesondere durch Piperazin. Berl. klin. Wochenschrift, 29, 381 (1892), also

Ibid. M. Mendelsohn in discussion of P. Biesenthal's article, Präparate künstlicher Gicht und Präparate geheilter künstlicher Gicht. Berl. med. Gesell., 19 July, 1893; Berl. klin. Wochenschrift, 30, 830 (1893).

that an aqueous solution of piperazin dissolves uric acid, but found that a urinary solution of piperazin does not dissolve uric acid. Ortowski [1] confirmed the experiments of Mendelsohn and Meisls on piperazin, and found that lysidin and uricedin behave in the same way, that is, an aqueous solution dissolves uric acid, a urinary solution does not. Meisls,[2] too, found that a urinary solution of uricedin does not dissolve uric acid stones. Mendelsohn,[3] Ortowski,[1] and Casper [4] found further that the urine of patients to whom piperazin has been given does not dissolve uric acid stones. Casper [4] found the same true for lysidin, and Ortowski [1] for lysidin and uricedin. Mendelsohn [3] found that even an aqueous piperazin solution takes a long time to dissolve bladder stones of uric acid. He did not find this drug of any clinical value in uric acid calculi.[5] Goodbody [6] is the only experimenter who states that piperazin or lysidin makes urine a better solvent for uric acid. His results do not show this, however. The amount of uric acid excreted is about the same in both cases. Weintraud [7] could not find that the administration of lysidin has any effect on the precipitation of uric acid. The statement of Ewald [8] that sidonal (the quinic acid salt of piperazin) and of Grawitz [9] and others that lysidin is clinically good in cases of uric acid stones and gravel cannot be accepted as evidence of the chemical action of these compounds, whatever clinical value they may have.

As we have seen, we should not expect that the alkalies, organic or inorganic, would have any effect on the dissolving power of cold urine for uric acid when uric acid normally precipitates

[1] W. Ortowski. Vergleichende Untersuchungen über Urotropin, Piperazin, Lysidin, Uricedin, und Natron bicarbonicum bei der harnsäuren Diathese. Zeitschr. für klin. Med., 40, 331 (1900).

[2] W. Meisls. Einige Versuche mit Uricedin. Pester med.-chir. Presse., 30, 684 (1894).

[3] M. Mendelsohn. Ueber Harnsäurelosung insbesondere durch Piperazin. Berl. klin. Wochenschrift, 29, 384 (1892).

[4] L. Casper. Ueber einiger Eigenschaften und Indikationen des Urotropins. Deutsche med. Wochenschrift, Ther. Beit., 75 (1897).

[5] M. Mendelsohn. Discussion of P. Biesenthal's article, Präparate künstlicher Gicht und Präparate geheilter künstlicher Gicht. Berl. med. Gesell., 19 July, 1893; Berl klin. Wochenschrift, 30, 830 (1893).

[6] F. Goodbody. The action of lysidin and piperazin as uric acid solvents. Brit. Med. Journ. (1896), II, 901.

[7] W. Weintraud. Ueber die Einfluss des Nucleins der Nahrung auf die Harnsäurebildung, 32, 405 (1895).

[8] Ewald. Discussion of Blumenthal's article, Ueber Sidonal, ein neues Gichtmittel. Verhandl. des Vereins für innere Med., Berl., 19, 480 (1899–1900).

[9] E. Grawitz. Beobachtungen über ein neues harnsäurelosendes Mittel. Deutsche med. Wochenschrift, 20, 786 (1894).

from it. The only effect would be to decrease the amount of uric acid which is precipitated before equilibrium is reached. Neumayer [1] has, in fact, shown that the administration of lysidin, or Na_2CO_3 decreases the free uric acid. For therapeutic ends, however, it is the dissolving power of urine for uric acid at the body temperature that we wish to affect. We have seen that Tunicliffe and Rosenheim [2] showed that the addition of piperidine, piperazin, or lysidin to a normal urine increases its dissolving power for uric acid at the body temperature. But a urine which deposits uric acid while still warm in the body is comparable in this respect with a cold normal urine. This is the kind of urine with which we have to deal in cases of uric acid gravel. Alkalies, then, unless in large quantities, have almost no effect on the dissolving power of such a urine for uric acid even at the body temperature.

According to Neumayer,[3] beer and white wine decrease the solvent power of the urine for uric acid; red wine and pure alcohol have no effect.

It will be well to speak here of Haig's [4] views concerning the uric acid in the urine. According to this author, the quantity of uric acid in the urine varies inversely as the acidity. By the quantity of uric acid, Haig means the value of the ratio of the quantity of uric acid to the quantity of urea. With our present knowledge of the metabolism of uric acid, we can see that the quantity of each of these substances can be varied independently by controlling the food, so that the physiological significance of the value of this ratio can be but little. Haig used the inaccurate Haycraft method for determining uric acid, and an inaccurate method for the determination of the acidity of the urine, so that we can place but little dependence upon his results.

Herringham and Davies [5] could find no relation between the acidity of urine (determined by titration) and the value of the ratio *uric acid* : *urea*. They used the Salkowski method

[1] H. Neumayer. Discussion in d. Versammlung des 14t Kongr. für innere Med., 424 (1896).

[2] F. Tunicliffe and O. Rosenheim. Piperidine as a Uric Acid Solvent, a comparative study. Lancet (1898), 2, 198.

[3] H. Neumayer. Ueber die Therapie der harnsäuren Diathese. Verhandl. des aerztlicher verein in München, 9 März, 1898. Deutsche med. Wochenschrift, 24, vereins Beilage, 60 (1898).

[4] Haig. Uric Acid as a Factor in the Causation of Disease. London, 1896.

[5] W. Herringham and H. Davies. On the Secretion of Uric Acid and Urea. Journ. of Physiol., 12, 475 (1891).

for the determination of uric acid. Herringham and Groves,[1] Schreiber and Waldvogel,[2] Schreiber and Zaudy,[3] and Strauss [4] found that there is no constant relation between the quantity of uric acid in the urine and the acidity of the urine (determined by titration). We should, of course, expect that the quantity of uric acid in the urine and the acidity of the urine could be varied independently.

The poor results obtained from the alkalies in the treatment of uric acid gravel and calculi has led to the use of certain drugs which unite with uric acid to form organic compounds which are not salts and which, therefore, will hold the uric acid in solution even in an acid urine. The first of this class of bodies to be used was urea. On the basis of Rüdel's [5] statement that urea forms a compound with uric acid which is soluble in water, and from which acids do not precipitate the uric acid, this compound has been introduced as a therapeutic agent. Rosenfeld,[6] for example, obtained good clinical results from urea; others, Neumayer,[7] for example, poor results. We have already seen that His [8] and Klemperer [9] proved Rüdel's statement to be erroneous.

His [10] showed that in the creatinin urate of Klemperer,[9] which at first was thought to be a non-electrolyte, creatin merely acts like any other alkali.

Urotropin (hexamethylentetramine) was introduced as a

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[1] W. Herringham and E. Groves. On the Secretion of Uric Acid, Urea, and Ammonia. Journ. of Physiol., 12, 478 (1891).

[2] Schreiber und Waldvogel. Beiträge zur Kenntniss der Harnsäureausscheidung unter physiologischen und pathologischen Verhältnisse. Arch. für exp. Path. u. Pharmak., 42, 69 (1899).

[3] Schreiber und Zaudy. Zur Wirkung der Salicylpräparate insbesondere auf die Harnsäure und die Leukocyten. Deutsche Arch. für klin. Medizin, 62, 242 (1899).

[4] J. Strauss. Ueber die Einwirkung des kohlensäuren Kalkes auf den menschlichen Stoffwechsel, ein Beitrag zur Therapie der harnsäuren Nierenconcrementen nebst Bemerkungen über Alloxurkörperausscheidung. Zeitschr. für klin. Medizin, 31, 493 (1896).

[5] Rüdel. Zur Kenntniss der Lösungsbedingungen der Harnsäure in Harn. Arch. für exp. Path. u. Pharmak., 30, 469 (1892).

[6] G. Rosenfeld. Zur Diagnose und Therapie der Uratdiathese. Centralblatt für innere Medizin, 16, 673 (1895).

[7] H. Neumayer. Ueber die Therapie der harnsäuren Diathese. Verhandl. des aerztlicher verein in München, 9 März, 1898. Deutsche med. Wochenschrift, 24, vereins Beilage, 60 (1898).

[8] W. His. Physikalisch-chemische Untersuchungen über das Verhalten der Harnsäure und ihrer Salze in Lösungen. Verhandl. der 18t Kongr. für innere Med., Wiesbaden, 425 (1900).

[9] G. Klemperer. Harnsäure Kreatinin eine wasserlöslich Harnsäureverbindungen. Fortschritte Med., 19, 328.

[10] W. His. Die Harnsäureablagerungen des Körpers und die Mittel zu ihrer Lösung. Therapie der Gegenwart, Neue Folge, 3, 434 (1901).

therapeutic agent by Nicolaier.[1] It was found to decompose in the body and appear in the urine, in part, at least, as formaldehyde by Citron,[2] Ortowski,[3] Cammidge,[4] and His.[5] Weber, Pott, and Tollens[6] found that formaldehyde and uric acid unite to form a compound which is not a salt. Löbisch[7] confirmed this discovery, and attributed the action of urotropin to the breaking up of this compound into formaldehyde. His[5] came to the same conclusion, and found further that the compound of formaldehyde is not a salt. The uric acid is not precipitated from a solution of this compound by acids.

Nicolaier,[8] Tánago,[9] Ortowski,[10] and Levison[11] found that the urine of patients to whom urotropin had been administered has the power of dissolving uric acid. These authors, and also Löbisch,[7] have found this drug clinically good in cases of uric acid stones and gravel. Tunicliffe and Rosenheim[12] found that the addition of urotropin itself to a urine increases slightly the solvent power of the urine for uric acid. According to Rosenfeld and Orgler,[13] urotropin does not always make a urine a better

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[1] A Nicolaier. Ueber die therapeutische Verwendung des Urotropin (Hexamethylentetramine). Deutsche med. Wochenschrift, 21, 541 (1895).

[2] A. Citron. Administration of Urotropine and Its Effects upon the Urine. The Therapist, 8, 115 (1896), also

Ibid. Monatsber. über die Gesammtleistungen auf d. Gebiete d. Krankh. d. Harn- und Sexualorgane, III, 2 (1898).

[3] W. Ortowski. Ueber die bactericiden Eigenschaften des Urotropin und seine Anwendung bei Cystitis. Petersbourg (1899).

[4] P. Cammidge. Urotropine as a Urinary Antiseptic. Lancet (1901), 1, 174.

[5] W. His. Die Harnsäureblagerungen des Körpers und die Mittel zu ihrer Lösung. Vortrag. auf der Versamml. deutsch. Naturforscher und Aerzte in Hamburg, 25 Sept. 1901. Therapie der Gegenwart, Neue Folge, 3, 434 (1901).

[6] K. Weber, R. Pott, und B. Tollens. Ueber Verbindungen von Fromaldehyde und Harnsäure. Ber. der Dtsch. chem. Gesell., 30, 2514 (1897), also

K. Weber und B. Tollens. Ueber die Einwirkung von Formaldehyde auf Harnsäure. Liebig's Ann., 299, 340 (1898).

[7] W. Löbisch. Ein Fall von Pyelitis calculosa urica behandelt mit Urotropin. Wien. klin. Wochenschrift, 10, 304 (1897).

[8] A. Nicolaier. Experimentelle und Klinisches über Urotropin. Zeitschr. für klin. Med., 38, 356 (1899).

[9] M. Tánago. Pharmacologische Behandlung der harnsäuren Diathese und besonders der Lithiasis urica. El Siglo Medico, 2270–1, June 27 and July 4, 1897.

[10] W. Ortowski. Vergleichende Untersuchungen über Urotropin, Piperazin, Lysidin, Uricedin, und Natron bicarbonicum bei der harnsäuren Diathese. Zeitschr. für klin. Med., 40, 331 (1900).

[11] F. Levison. Werthvergleichung der Heilmittel der harnsäuren Diathese. Ugeskrift for Laeger, (1896–97).

[12] F. Tunicliffe and O. Rosenheim. Piperidine as a Uric Acid Solvent, a comparative study. Lancet (1898), 2, 198.

[13] Rosenfeld und Orgler. Zur Behandlung der harnsäuren Diathese. Centralblatt für innere Medizin, 17, 42 (1896).

solvent for uric acid. More experiments are needed before we can conclude that urotropin is a valuable therapeutic agent in cases of uric acid calculi. It may be mentioned incidentally that the toxic effects attributed by some writers to this drug in certain cases have been found by Coleman [1] to occur but rarely.

It will be remembered (see p. 69) that Kossel, Minkowski, and Goto found that nucleic acid, and Kossel and Goto that the so-called thymic acid have the power of uniting with uric acid to form compounds which are not salts, and therefore not decomposed by acid. These authors recommended that nucleic and "thymic" acid might be tried as therapeutic agents. Nucleic acid has the disadvantage of containing purin bodies, which increase the excretion of uric acid, and it seems to be impossible to get a "thymic" acid free from purin bases. Besides, although these acids may dissolve uric acid in a test tube, they will decompose in the body and therefore not reach the urine in such a form as to be of any value.

There are, then, no substances which have been shown to have any effect on the solubility of uric acid in the urine.

The Effect of Drugs on the Solubility of Uric Acid in the Blood

According to the belief of Haig [2] and many others, when the blood becomes overcharged with uric acid, either on account of the formation of large quantities of uric acid, or on account of decreased alkalinity, the uric acid deposits in some part of the body. If the deposit occurs in the joints, we get rheumatism or gout. To treat this condition, Haig decreases the foods which are believed to give excessive uric acid, and administers alkalies to increase the alkalinity of the blood in order to keep uric acid in solution and to dissolve concretions already formed. He says,[3] "We have only now to suppose what I expect no one will dispute, that a dose of acid will diminish the alkalescence of the blood and tissue fluids, and also of the liver and spleen, and that

[1] W. Coleman. The Toxic Actions of Urotropin, with Report of a Case of Hematuria and Hemoglobinurea, following a Dose of Seven and One-Half Grains. Med. News, 83, 393 (1903).

[2] A. Haig. Uric Acid as a Factor in the Causation of Disease. London, 1896.

[3] *Ibid.* Variations in the Excretion of Uric Acid produced by Administration of Acids and Alkalies. Journ. of Physiol., 8, 211 (1887).

a dose of alkali will produce the reverse effect, to see why and how they may alter the excretion of uric acid in the way I have shown that they do." The view, first suggested by Wollaston,[1] that by the administration of alkalies we can dissolve concretions of sodium acid urate in the body, has served as the basis for those theories of Haig which are so widely adopted and which attribute so many diseases to uric acid. This view is certainly open to dispute.

Höber [2] was the first to determine the alkalinity of the blood expressed in terms of the concentration of the hydroxyl ions. He found it to vary from 0.22×10^{-5} to 0.9×10^{-5}.

More recent determinations by Höber [3] give much lower figures, viz.: 0.7×10^{-7} to 2.0×10^{-7}. Farkas,[4] who has likewise determined the concentration of the hydroxyl ions in the blood, obtained about the same results, viz.: $1. \times 10^{-7}$ to $3. \times 10^{-7}$. This author showed that Höber's higher results are due to a slight error in his method.[5] Fraenckel [6] obtained still lower values.

All other determinations have been made by titration methods or by other methods which give the "potential" alkalinity, that is, the concentration of the hydroxyl ions available from the basic salts, such as alkaline sodium phosphate and sodium carbonate. The figures indicate that the alkalinity of the blood is very low, comparable in part with the alkalinity of very pure water which has hydroxyl ions to the extent of about $.8 \times 10^{-7}$ gram molecules per liter. The sulphuric acid formed by the oxidation of but a fifth of a milligram of sulphur would be enough to neutralize completely the alkalinity of the whole five liters of blood. Yet, in spite of the fact that considerable quantities of acid are continuously being formed by the oxidation of the sulphur and phosphorus of the body and food, and in other ways, and introduced into the blood, the blood is always alkaline. This indicates that there must be some regulating power which

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[1] Wollaston. On Gouty and Urinary Concrements. Phil. Transactions (1797), 388.

[2] R. Höber. Ueber die Hydroxylionen des Blutes. Pflüger's Archiv, 81, 522 (1900).

[3] *Ibid.* Pflüger's Archiv, 99, 572 (1903).

[4] G. Farkas. Ueber die Konzentration der Hydroxylionen im Blutserum. Pflüger's Archiv, 98, 551 (1903).

[5] *Ibid.* Arch. für Physiol. (1903), Suppl., 517.

[6] P. Fraenckel. Eine neue Methode zur Bestimmung der Reaktion des Blutes. Pflüger's Archiv, 96, 601 (1903).

maintains the alkalinity of the blood.[1] Since, then, the introduction of large quantities of acid from within does not normally have any influence on the alkalinity of the blood, it seems hardly probable that we can directly influence the alkalinity of the blood in physiological cases by the introduction of small quantities of acids or alkalies from without. Freudberg [2] has found that the administration of from 4 to 8 grams HCl per day does not influence the alkalinity of the blood as determined by even titration methods, and Magnus-Levy [3] could not find that the administration of 18 grams HCl or 40 grams $NaHCO_3$ has any influence.

The next question is whether the addition of alkali or acid directly to blood serum would affect its power of dissolving uric acid. A precipitation of uric acid from blood will occur only when the concentration of the H ions and the negative uric acid ions, $\bar{U}$, is such that the value $C_H \times C_{\bar{U}}$ is greater than 206×10^{-12}. A precipitation of sodium acid urate will occur only when the concentration of Na and $\bar{U}$ are such that the value for k in the equation $C_{Na} \times C_U = k$ is exceeded. On addition of acid to a blood serum, the H ions from the acid will unite with the OH ions in the serum to form undissociated HOH. On neutralization of the "actual" OH ions, new OH ions are set free to reëstablish equilibrium. This is shown by the fact that the titration methods give blood such a high alkalinity compared with the electrochemical methods. The addition of acid, then, does not affect the values C_H, C_U, or C_{Na} until enough acid is added to make the blood practically neutral. We cannot, of course, reach this point with the blood in the living body.

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[1] Among the different conditions of equilibrium in the blood we have

$$\frac{C_H \times C_{HPO_4}}{C_{H_2PO_4}} = k_2 \text{ and } C_H \times C_{OH} = k_1. \quad \text{Then } \frac{k_2}{k_1} = K = \frac{C_{HPO_4}}{C_{OH} \times C_{H_2PO_4}}.$$

Therefore, when C_{OH} decreases by addition of acid, C_{HPO_4} must decrease or $C_{H_2PO_4}$ increase to maintain equilibrium. The reaction: $HPO''_4 + HOH = H_2PO'_4 + OH'$, whereby HPO_4 decreases and H_2PO_4 increases, would reëstablish equilibrium. In the same way, from the equation

$$\frac{k_3}{k_1} = K = \frac{C_{HCO_3}}{C_{OH} \times C_{H_2CO_3}}, \text{ where } k_3 = \frac{C_H \times C_{HCO_3}}{C_{H_2CO_3}}$$

we can see that the reaction $HCO'_3 + HOH = H_2CO_3 + OH'$ would also re-establish equilibrium after disappearance of OH ions. In either case the potential hydroxyl ions come directly from the water, but are due to the presence of salts of strong acids and weak bases.

R. Höber. Die Aciditat des Harns vom Standpunkt der Ionenlehre. Beiträge z. chem. Physiol. u. Path., 3, 525 (1903).

[2] H. Freudberg. Ueber den Einfluss von Säuren und Alkalien auf die Alkalescenz des Blutes und die Reaktion des Harnes. Virchow's Archiv, 125, 566 (1891).

[3] A. Magnus-Levy. Harnsäuregehalt und Alkalescenz des Blutes in der Gicht. Verhandl. des 16t Kongr. für innere Med., 266 (1898).

The concretions in case of gout are of sodium acid urate, so that it is only the solubility of sodium acid urate in the blood with which we have to deal. Increasing C_{OH} by making the blood more alkaline does not change the values for C_{Na} or $C_{\overline{U}}$. We cannot, therefore, increase the dissolving power of the blood for sodium acid urate even if we do increase the alkalinity of the blood.

The experimental proof that addition of acid does not precipitate uric acid or urate from a blood serum was given by Luff.[1] This author found that addition of enough HCl or tartaric acid to neutralize one half, one fourth, or even three fourths the alkalinity of the blood does not bring about a precipitation of uric acid or urate from a concentrated solution of uric acid in blood serum.

The experiments of Tunicliffe and Rosenheim[2] showing that the addition of organic bases to blood serum increases its solvent power for uric acid do not come into consideration, since it is sodium acid urate and not uric acid that we have to deal with in gout.

Klemperer[3] has shown that the alkalinity of the blood (determined by titration) is not decreased in gout, and, further, that the blood is not saturated with uric acid. It can, in fact, dissolve about as much uric acid as normal blood, so that there is no need of making the blood more alkaline or a better solvent for uric acid.

To sum up, then, first, there is no reason to believe that we can directly increase or decrease the alkalinity of the blood by the administration of alkalies or acid; second, a change in the alkalinity of the blood will not affect the solubility of sodium acid urate in it; third, the "potential" alkalinity of the blood and its power of dissolving sodium acid urate are not decreased in gout, so that there is no basis for trying to bring the alkalinity back to a normal condition or for attempts to make the blood a better solvent for uric acid.

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[1] A. Luff. (Goulstonian Lectures.) The Chemistry and Pathology of Gout Lancet (1897), 1, 857, 942, 1069.

[2] F. Tunicliffe and D. Rosenheim. Piperidine as a Uric Acid Solvent, a comparative study. Lancet (1898), 2, 198.

[3] G. Klemperer. Zur Pathologie und Therapie der Gicht. Deutsche med. Wochenschrift, 21, 665 (1895).

EFFECTS OF ALKALIES ON URIC ACID CONCRETIONS IN BIRDS

Certain authors have performed experiments on birds in the endeavor to show that the administration of alkalies increases the dissolving power of the blood and fluids of the body for uric acid. Ebstein [1] and others had shown that the administration of potassium chromate to hens and doves brought about the formation of concretions of uric acid in the kidneys similar to those formed when the ureters are tied. Kossa [2] found that aloin, sublimate, oxalic acid, carbolic acid, aceton, and other kidney poisons bring about the same result. This author attributed the formation of the concretions to slow destruction of the kidney functions. Similar concretions are found in hens when they are fed on meat for a long period. Biesenthal [3] found that the administration of potassium chromate does not bring about uric acid concretions in hens if piperazin is given at the same time. Richter [4] performed two series of experiments on birds. In one series, potassium chromate alone was administered. In the other series both sidonal (quinate of piperazin) and potassium chromate were given. Concretions of uric acid occurred in the kidneys of the birds used in the first series. No concretions occurred in the birds used in the second series. According to Hoffmann,[5] no concretions of uric acid occur in hens after meat-eating if certain alkaline spring waters are administered at the same time.

Some authors have concluded that these experiments indicate that alkalies are good therapeutic agents in gout, and that the good action can be attributed to a solution of the uric acid in the joints. Such conclusions are not warranted. Uric acid holds a different position in the metabolism of birds from that which

[1] Ebstein. Die Natur und Behandlung der Gicht. Wiesbaden (1882).

[2] J. Kossa. Künstliche Erzeugung der Gicht durch Gifte. Arch. internat. de Pharmacodynamie, 5, 97 (1898); Maly's Jahresb. über die Fortschritte der Thierchemie, 28, 678 (1898).

[3] P. Biesenthal. Wirkung des Piperazin bei künstlich erzeugten Harnsäureablagerungen im thierischen Organismus. Verhandl. der Berliner med. Gesell., July 12, 1893; Berl. klin. Wochenschrift, 30, 805 (1893), also

Ibid. Ueber den Einfluss des Piperazin auf die harnsauren Diathese. Virchow's Archiv, 137, 51 (1894).

[4] P. Richter. Ueber die experimentelle Prüfung sogennanter "Gichtmittel" im Allgemeinen und über die Chinasäure und das chinasäure Piperazin im Besonderer. Charité Annalen, 25, 197 (1900).

[5] P. Hoffmann. Beiträge zur Kenntniss der Kronenquelle zu Salzbrunn in Schlesien Breslau (1901).

it holds in the metabolism of mammals. We cannot consider the conditions brought about in birds by potassium chromate and other kidney poisons analogous to real gout. According to Biesenthal,[1] the chromate causes destruction of the parenchyma of the kidney. We have then a retention of the end product of nitrogenous metabolism due to the destruction of the kidney. This is a condition more nearly approaching uremia in man. If piperazin prevents the formation of the concretions, it is for some unknown reason, and it is undoubtedly not due to any effect on the dissolving power of the blood for uric acid.

It is even very doubtful if the administration of alkalies does prevent the formation of concretions in birds after injection of chromate. According to Meisls, although piperazin prevents the concretions, neither $LiCO_3$,[2] nor uricedin[3] prevents them. Aujeszky and Donogány,[4] too, found that uricedin does not prevent the formation of concretions after chromatic injections. According to Ortowski,[5] neither urotropin, lysidin, piperazin, $NaHCO_3$ nor uricedin has any effect in preventing the concretions. According to Kossa,[6] piperazin makes them worse.

The Effect of Drugs on the Size of the Uric Acid Excretion

The effect on the excretion of uric acid of those drugs found clinically good in gout has been studied by numerous physiologists. An increased excretion of uric acid after a drug may be due to an increase in the amount either of the endogenous or the exogenous uric acid formed from nucleins, or to a decrease in the amount of uric acid oxidized, or, possibly, to a formation of uric acid from some other source. A decreased excretion of uric acid may be due, on the other hand, to a decrease in the forma-

[1] P. Biesenthal. Wirkungen des Piperazin bei künstlich erzeugten Harnsäureablagerungen im thierischen Organismus. Verhandl. der Berliner med. Gesell., July 12, 1893; Berl. klin. Wochenschrift, 30, 805 (1893).

[2] W. Meisls. Experimente mit Piperazin und anderen uratlösenden Mitteln. Ungarisches Arch. für Med., 1, 364 (1893); Maly's Jahresb über die Fortschritte der Thierchemie, 23, 582 (1893).

[3] *Ibid.* Einige Versuche mit Uricedin. Pester med.-chir. Presse, 30, 684 (1894).

[4] A. Aujeszky und Z. Donogány. Ueber die uratlösende Wirkung des Uricedin. Pester med.-chir. Presse, 30, 681 (1894).

[5] W. Ortowski. Vergleichende Untersuchungen über Urotropin, Piperazin, Lysidin, Urecidin, und Natron bicarbonicum bei der harnsäuren Diathese. Zeitschr. für klin. Medizin, 40, 331 (1900).

[6] J. von Kossa. Künstliche Erzeugung der Gicht durch Gifte. Arch. internat. de Pharmacodynamie, 5, 97 (1898); and Maly's Jahresb. über die Fortschritte der Thierchemie, 28, 678 (1898).

tion of uric acid, or to the fact that a larger amount is oxidized than normally. So long as we do not know the significance of decreased and increased excretion of uric acid after drugs, and in what the abnormalities in the metabolism of uric acid consist in gout, there is no reason for giving a drug in gout because of its effect on the amount of uric acid in the urine.

If, on the other hand, alkalies, for example, are found clinically good in gout, the good effect cannot be attributed to the fact that they make the blood a better solvent for uric acid, that they cause an " alkaline tide " that " sweeps out " the uric acid, to use Haig's terms. Neither can we say that the alkalies decrease the production or hasten the oxidation of uric acid. The good action, if there is any, must be attributed to some other influence on the general metabolism.

ALKALIES

Gorsky [1] found a slight increase in the excretion of uric acid after $LiCO_3$, and Zagari and Pace [2] after other alkalies. Salkowski [3] observed increased excretion of uric acid in dogs after administration of sodium acetate, which oxidizes to carbonate. Axenfeld,[4] who used the Haycraft method for the determination of uric acid, observed sometimes a very slightly increased excretion of uric acid after ammonium tartrate. According to Dapper,[5] Vogel,[6] and Bain,[7] piperazin causes a slight increase in the excretion of uric acid, and according to Bain,[7] lysidin has the same effect. According to Gilardoni,[8] alkaline water increases the excretion of uric acid.

[1] G. Gorsky. Ueber den Einfluss des Lithiumcarbonate auf den Stickstoffwechsel bei Gesunden. Centralblatt für der med. Wissen., 28, 27 (1890).

[2] G. Zagari e D. Pace. La genesi dell' acido urico e la gotta in riguardo alla patogenesi e all' indirizzo terapeutico. Napoli, 1897. Centralblatt für innere Medizin, 190, 816 (1898).

[3] E. Salkowski. Ueber die Grösse der Harnsäureäusscheidung und den Einfluss der Alkalien auf dieselbe. Virchow's Archiv, 117, 590 (1889), and Spilker. Ueber den Einfluss der Alkalien auf den Stoffwechsel mit besonderer Berücksichtigung der Harnsäure. Inaug. Dissert., Berl., 1890.

[4] D. Axenfeld. Intorno alla transformazione dei sali di ammonio in urea nell' organismo. Annali di chimica e di farmacologia, p. 172 (1888), and Maly's Jahresb. über di. Fortschritte der Thierchemie, 18, 122 (1888).

[5] K. Dapper. Ueber Harnsäureausscheidung beim gesunden Menschen unter verscheidenen Ernährungsverhältnissen. Berl. klin. Wochenschrift, 30, 617 (1893).

[6] L. Vogel. In von Noorden's Beiträge zur Lehre von Stoffwechsel. Berl. (1894), 2, 113.

[7] W. Bain. The Influence of Some Modern Drugs on Metabolism in Gout. Brit. Med. Journ. (1903), 1, 243.

[8] A. Gilardoni. Beitrag über den Einfluss des alkalischen mineralwassers auf Stickstoff- und Harnsäureausscheidung. Therap. Monatsh., 18, 69 (1904).

On the other hand, Laveran and Millon [1] found that sodium potassium tartrate, which oxidizes in the body to carbonate, decreases the excretion of uric acid. Moss [2] found that sodium acetate likewise decreases the excretion of uric acid. Laveran and Millon and Moss used the inaccurate Heinz method for the determination of uric acid. Stadelmann [3] found that alkalies cause a slight decrease in the excretion of uric acid. Munch [4] found the excretion of uric acid decreased after doses of three or four grams Na_2CO_3 per day. According to Laquer,[5] the excretion of uric acid is decreased after drinking Ems spring water, which contains the carbonates of both sodium and potassium.

Lo Monaco [6] found that the excretion of uric acid is decreased after drinking water containing $CaH_2(CO_3)_2$. According to Aujeszky and Donogány,[7] uricedin causes a decrease in the excretion of uric acid, but their results do not seem to indicate that the drug has any effect in this direction. His [8] observed a very slightly decreased excretion of uric acid after $LiCO_3$.

Clar [9] found first a slight increase and then a decrease in the excretion of uric acid after Na_2CO_3. According to Umber,[10] $NaHCO_3$ increases the excretion of purin bases. According to Determeyer and Büttner,[11] certain alkaline spring waters (Oberbrunnen) cause decreased excretion of uric acid in health, but increased uric acid in the uric acid diathesis.

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[1] Laveran et Millon. Mémoire sur le passage de quelques médicaments dans l'économie animale, et sur les modifications qu'ils y subissent. Annales de chimie et de physique, 3 ser., XII, 135 (1844).

[2] Moss. On the Action of Potash, Soda, Lithia, Lead, Opium, and Colchicum on the Urine. Amer. Journ. of Med. Sciences, XLI, 384 (1861).

[3] E. Stadelmann. Ueber den Einfluss der Alkalien auf den menschlichen Stoffwechsel. Verhandl. des 9t Kongr. für innere Medizin, Wiesbaden, p. 381 (1890).

[4] Munch. Wirkung des kohlensäures Natrons auf den menschlichen Körper, insbesondere den Stoffwechsel. Arch. d. wissenschaftisch. Heilk., 6, 369.

[5] W. Laquer. Der Einfluss der Emser Quellen auf die Harnsäureausscheidung des Menschen. Berl. klin. Wochenschrift, 40, 586 (1903).

[6] D. Lo Monaco. Gli effecti della acque alcaline sul consumo azodato e sulla formazione dell' acido urico. Policlinico, 3, 345 (1896); Schmidt's Jahrb., 253, 124 (1897).

[7] A. Aujeszky und Z. Donogány. Ueber die uratlösende Wirkung des Uricedin. Pester med.-chir. Presse, 30, 681 (1894).

[8] W. His. Die Ausscheidung von Harnsäure im Urin der Gichtkranken mit besonderer Berücksichtigung der Anfallszeiten und Behandlungsmethoden. Deutsche Arch. für klin. Medizin, 65, 156 (1900); also

Ibid. Untersuchungen an Gichtkranken. Wien. med. Blätter, 19, 291 (1896).

[9] C. Clar. Ueber den Einfluss des kohlensäuren Natrons aud die Stickstoffausscheidung beim Menschen. Centralblatt für die med. Wissen., 26, 466 (1888).

[10] F. Umber. Ueber den Einfluss nucleinhaltiger Nahrung auf die Harnsäurebildung. Zeitschr. für klin. Med., 29, 174 (1896).

[11] Determeyer und Büttner. Zur Therapie der harnsäuren Diathese. Deutsche med. Wochenschrift, 27, 336 (1901).

The bulk of the evidence seems to indicate that the alkalies neither decrease nor increase the excretion of uric acid. Thus, neither Spilker,[1] Kemptner,[2] Laquer,[3] nor Rosenfeld[4] could observe that the administraton of alkalies has any effect on the excretion of uric acid in man. According to Severin,[5] the administration of from two to four grams Na_2CO_3 per day does not affect the quantity of uric acid excreted. Herrmann[6] could not observe that sodium or potassium tartrate which oxidize to carbonates, nor Weiss[7] that the potassium salts of other plant acids have any effect on the excretion of uric acid, and Bain could not find that piperazin tartrate has any effect. After the administration of an alkaline spring water (Tarasperwasser, Luciusquelle), containing the bicarbonates of sodium, potassium, and magnesium, Leva[8] found that the excretion of uric acid is not changed, and after Fachinger and Offenbacher waters, which contain $NaHCO_3$, Schreiber and Zaudy[9] found that the excretion of uric acid is not changed. His[10] could not find any effect on the excretion of uric acid from $NaHCO_3$, Fachinger water, lysidin, piperazin, or uricedin. Levison,[11] Ebstein and Sprague,[12] Vogel,[13] and Biesenthal

[1] E. Spilker. Ueber den Einfluss der Alkalien auf den Stickstoffwechsel mit besonderer Berücksichtigung der Harnsäure. Inaug. Dissert., Berlin, 1889.

[2] Kemptner. Ueber die Stickstoff- und Harnsäureausscheidung bei Zufuhr von kohlensäuren resp. citronsäuren Natron. *From* Stadelmann. Ueber den Einfluss der Alkalien auf den menschlichen Stoffwechsel. Stuttgart, 1890.

[3] Laquer. Ueber die Ausscheidungsverhältnisse der Alloxurkörper im Harne von Gesunden und Kranken. Verhandl. des 14t Kongr. für innere Medizin, 333 (1896).

[4] G. Rosenfeld. Grundzüge der Berhandlung der harnsäuren Diathese. Verhandl. des 14t Kongr. für innere Medizin, 318 (1896).

[5] Severin. Ueber die Einwirkung des kohlensäures Natrons auf den Gehalt des Harns an Harnsäure. Inaug. Dissert. (1868), Marburg.

[6] A. Herrmann. Ueber die Abhangigkeit der Harnsäureausscheidung von Nahrungs- und Genussmitteln mit Rücksicht auf die Gicht. Deutsche Arch. für klin. Medizin, 43, 273 (1888).

[7] J. Weiss. Eine neue Methode der Behandlung der harnsäuren Diathese. Berl. klin. Wochenschrift, 36, 297 (1899).

[8] J. Leva. Ueber die Einwirkung des Tarasperwassers (Luciusquelle) auf den Stoffwechsel. Berl. klin. Wochenschrift, 31, 260, und 291 (1894).

[9] Schreiber und Zaudy. Zur Wirkung der Offenbacher Kaiser Friedrichs-Quelle. Zeitschr. für diät und physikal. Therapie, 2, 136 (1899).

[10] W. His. Untersuchungen an Gichtkranken. Wien. med. Blätter, 19, 291 (1896), and *Ibid.* Die Ausscheidung von Harnsäure im Urin der Gichtkranken mit besonderer Berücksichtigung der Anfallszeiten und bestimmter Behandlungsmethoden. Deutsche Arch. für klin. Medizin, 65, 156 (1900).

[11] C. Levison. Ueber den Einfluss einiger Medicamente auf Harnsäureausscheidung und Leukocytenzahl. Dissert., Bonn (1897).

[12] W. Ebstein und C. Sprague. Notiz, betreffend die therapeutische Anwendung des Piperazin. Berl. klin. Wochenschrift, 28, 341 (1891).

[13] Vogel. Ueber den Stoffwechsel bei Gichtkranken. Verhandl. der Berl. physiol. Gesellsch., 17 Feb., 1893, und Du Bois Archiv, 377 (1893).

and Schmidt [1] found that piperazin, and Klemperer and Ziesig [2] that lysidin does not affect the excretion of uric acid. Meisls [3] showed that uricedin, and Strauss [4] that $CaCO_3$, has no effect on the excretion of uric acid.

WATER AND NEUTRAL SALT SOLUTIONS

The drinking of large quantities of water does not seem to have any effect on the amount of uric acid excreted in man, according to Kusmanoff,[5] Schöndorff,[6] Hopkins and Hope,[7] Schreiber,[8] and Gilardoni.[9] Only Genth,[10] who used an inaccurate method of analysis, and who found decreased uric acid after water drinking, observed any effect of water drinking. In cases of heart disease, the amount of uric acid excreted per day was somewhat dependent upon the quantity of urine excreted in the experiments of Kobler [11] and Husches.[12] Unfortunately, Kobler's patient was taking digitalis during the experiment. Laquer [13] seemed to find a relation between the quantity of water taken and the amount of purin bases excreted. He used, however, the inaccurate Krüger-Wulff method of determination. Burian and Schur [14] found that the excretion of uric acid is increased in dogs by diuresis.

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[1] Biesenthal und Schmidt. Piperazin bei Gicht und Steinleiden. Berl. klin. Wochenschrift, 28, 1231 und 1214 (1891).

[2] Klemperer und Ziesig. Bericht über die Behandlung von drei Gichtkranken mit Lysidin. Klemperer's Untersuchungen (1896).

[3] W. Meisls. Einige Versuche mit Uricedin. Pester med.-chir. Presse, 30, 684 (1894).

[4] J. Strauss. Ueber die Einwirkung des kohlensäuren Kalkes auf den menschlichen Stoffwechsel, ein Beitrag zur Therapie der harnsäuren Nierenconcrementen nebst Bemerkungen über Alloxurkörperausscheidung. Zeitschr. für klin. Med., 31, 493 (1896).

[5] A. Kusmanoff. Die Ausscheidung der Harnsäure bei absoluter Milchdiät. Inaug. Dissert., Dorpat, 1885.

[6] B. Schöndorff. Ueber den Einfluss des Wassertrinkens auf die Ausscheidung der Harnsäure. Dissert., Bonn, 1890, and Pflüger's Archiv, 46, 529 (1890).

[7] F. Hopkins and W. Hope. On the Relation of Uric Acid to Diet. Journ. of Physiol., 23, 271 (1898).

[8] Schreiber. Ueber die Harnsäure, 38, Stuttgart, 1899.

[9] A. Gilardoni. Beitrag über den Einfluss des alkalischen Mineralwassers auf Stickstoff- und Harnsäureausscheidung. Therap. Monatsh., 18, 69 (1904).

[10] Genth. Untersuchungen über den Einfluss des Wassertrinkens auf den Stoffwechsels. Wiesbaden, 1856.

[11] G. Kobler. Ueber einiger Bezeihungen der Diurese zur Harnstoff- und Harnsäureausscheidung, insbesondere bei den Compensationsstörungen der Herzkranken. Wien. klin. Wochenschrift, 353 and 375 (1891), and Maly's Jahresb. über die Fortschritte der Thierchemie, 21, 431 (1891).

[12] Husches. Ueber der N-Bilanz in den verschiedenen Stadien der Herzkrankheiten. Zeitschr. für klin. Med., 26, 44 (1894).

[13] B. Laquer. Ueber die Ausscheidungsverhältnisse der Alloxurkörper im Harne von Gesunden und Kranken. Verhandl. des 14t Kongr. für innere Medizin, 333 (1896).

[14] R. Burian und H. Schur. Ueber die Stellung der Purinkörper im Menschlichen Stoffwechsel. 2. Mitth. Pflüger's Archiv, 87, 239 (1901).

Dapper [1] could not find that the drinking of water containing common salt has any effect on the excretion of uric acid. Bencke,[2] who used the inaccurate Heinz method of determination, found the uric acid increased in two cases, and decreased in one case after use of water containing sodium chloride. After Friedrichschaller bitter water, which contains chiefly the sulphates and chlorides of sodium and magnesium, a decreased excretion of uric acid was found by Mosler [3] and by Markwald.[4] They used the Heinz method for determining uric acid. Seegen,[5] who used the Heinz method for analysis, and Ludwig,[6] who used an accurate method, found that the excretion of uric acid is diminished by Carlsbad water, which contains chiefly Na_2SO_4, Na_2CO_3, and NaCl.

It seems probable, then, that the amount of water taken has but little effect upon the quantity of uric acid excreted. The effect of water containing sodium chloride is very slight. Water containing sodium sulphate seems to cause a slight decrease in the excretion of uric acid.

SALICYLIC ACID

A great many observers have obtained good clinical results in gout from salicylic acid preparations. Only Noël-Paton[7] found decreased excretion of uric acid after administration of salicylic acid. He used dogs in his experiment. Kumagawa,[8] on the other hand, found that salicylic acid increases the excretion of uric acid in dogs. In man, salicylic acid has been found to produce an increase in the excretion of uric acid by Byasson,[9] Marrot,[10]

[1] Dapper. Ueber den Einfluss der Kochsalzquellen (Kissengen, Homburg) auf den Stoffwechsel beim Menschen und die sogennante " curgemässe " Diät. Zeitschr. für klin. Med., 30, 371 (1896).

[2] Bencke. Ueber Nauheimer Soolthermen, 1859.

[3] F. Mosler. Ueber die Wirkung des Friedrichshaller Bitterwasser. Arch. des Vereins für gemeinschaft. Arbeiten zur Förderung der Wissenschaft. Heilkunde, 5, 1 (1861).

[4] B. Markwald. Ueber die Wirkungen des Friedrichshaller Bitterwassers und seinen Einfluss auf den Stoffwechsel. Deutsche med. Wochenschrift, 12, 391 (1886).

[5] Seegen. Physiologisch-chemische Untersuchungen über den Einfluss des Karlsbader Mineralwassers auf den Stoffwechsel. Wien. med. Wochenschrift, 10, 321 and 340 (1860).

[6] V. Ludwig. Ueber den Einfluss des Karlsbader Wassers auf den Stoffwechsel. Centralblatt für innere Medizin, 17, 1153 und 1177 (1896).

[7] D. Noël-Paton. On the Nature of the Relationship of Urea Formation to Bile Secretion. Journ. Anat. and Physiol., 20, 114, 265 (1886).

[8] M. Kumagawa. Ueber die Wirkung einiger antipyretische Mittel auf den Eiweissumsatz im Organismus. Virchow's Archiv, 113, 134 (1888).

[9] H. Byasson. Etude sur la transformation de l'acide salicylique ingéré par l'homme. Jour. de Thérapeutique, 4, 721 (1877).

[10] E. Marrot. De l'action du salicylate de soude dans le rheumatisme aigu. Examin de l'urine et du sang. Arch. gén. de Méd., 7 sér., 3, 142 (1879).

Lecorché and Talamon,[1] See,[2] Lecorché,[3] Chopin,[5] Herter and Smith,[6] Tanszk and Vas,[7] F. Levi[illegible] Weidner,[10] C. Levison,[11] Lewandowski,[12] Singer,[13] Waldvogel,[15] and Schreiber and Zaudy.[16]

This high excretion of uric acid is attribu[illegible] to different causes. According to Levison, the salicylic acid increases the number [illegible] increased excretion of uric acid is parall[illegible]d leucocytosis. Schreiber and Zaudy[16] could[illegible] there is any relation between the number of leucoc[illegible]nd the excretion of uric acid. Haig and others attribute to salicylic acid the same action as they do to the alkalies. They believe that the salicylic acid dissolves the uric acid found in various parts of the body and "washes" it out. This cannot be so. Schreiber and Zaudy[16] found that if three grams salicylic acid per day are given for five days, there is at first an increased excretion of uric acid. This decreases in a few days to the normal amount. According to Haig, this is due to the fact that the uric acid in the body is com-

[1] Lecorché et Talamon. De l'action du salicylate de soude sur l'urée l'acide urique et l'acide phosphorique. Rév. mensuelle de méd. (1880).

[2] See. Husemann Arzneimittellehre 313 (1883).

[3] Lecorché. Traité de la Goutte, Paris (1884).

[4] E. Salomé. Ueber den Einfluss des salicylsauren Natrons auf die Stickstoff- und Harnsäureausscheidung beim Menschen. Schmidt's Jahrb., 209, 133 (1886), and Wien. med. Jahrb., 4, 463 (1885).

[5] Chopin. Ausscheidung der Salicylsäure. Bull. gén. de Thérap. (1889), Feb., and Maly's Jahresb. über die Fortschritte der Thierchemie, 19, 193 (1889).

[6] C. Herter and E. Smith. Observations on the excretion of uric acid in health and disease. N. Y. Med. Journ., June 4, 1892.

[7] F. Tanszk und B. Vas. Ueber den Einfluss einiger Antipyretica auf den Stoffwechsel. Ungar. Arch. f. Med., 1, 204 (1892), Maly's Jahresb. über die Fortschritte der Thierchemie. 22, 438 (1892).

[8] F. Levison. Die Harnsäure diathese. Berl. (1893).

[9] K. Bohland. Ueber den Einfluss des salicylsäuren Natrons auf die Bildung und Ausscheidung der Harnsäure. Centralblatt für innere Medizin, 17, 70 (1896).

[10] Weidner. Ueber die Einwirkung schweisstreibender und schweisswidriger mittel auf den Leucocytengehalt des Blutes beim Menschen. Inaug. Dissert., Bonn (1896).

[11] C. Levison. Ueber den Einfluss einiger medicamente auf Harnsäureausscheidung und Leukocytenzahl. Inaug. Dissert., Düsseldorf (1897).

[12] M. Lewandowski. Versuche über den Einfluss der Benzoesäure auf die Harnsäurebildung. Zeitschr. für klin. Med., 40, 202 (1900).

[13] H. Singer. Ueber Aspirin. Beiträge zur Kenntniss der Salicywirkung. Pflüger's Archiv, 84, 527 (1901).

[14] H. Ulrici. Ueber pharmakologische Beeinflussung der Harnsäureasusscheidung. Arch. für exp. Path. u. Pharm., 46, 321 (1901).

[15] Schreiber und Waldvogel. Beiträge zur Kenntniss der Harnsäureausscheidung unter physiologischen und pathologischen Verhältnissen. Arch. für exp. Path. u. Pharm., 42, 69 (1899).

[16] Schreiber und Zaudy. Zur Wirkung der Salicylpräparate, insbesondere auf die Harnsäure und die Leucocyten. Deutsche Arch. für klin. Medizin, 62, 242 (1899).

pletely "w[illegible]hed [illegible]. But, if on the sixth day the dose of salicylic acid is d[illegible] there is again an increase in the amount of uric acid exc[illegible]owing that Haig's explanation is wrong. According to J[illegible]e should not give salicylic acid in gout. He thinks that [illegible]ased excretion of uric acid after this drug indicates an incre[illegible]ormation which is bad for the gouty. It will be remem[illegible]hat Burian[1] found salicylic acid to increase the rate of [illegible]n by which uric acid is formed from the purin bases in [illegible]periments on autolysis; whether or no this has any bearin[illegible]e question we cannot say.

QUINIC ACID

We have already spoken of the theory of uric acid formation on which the use of quinic acid has been based. Briefly, the good clinical effects of the citron cure, cherry cure, and other fruit cures led to a search for the active principle in these fruits. According to Weiss, this is quinic acid [tetroxybenzoic acid, $C_6H_7(OH)_4COOH$], which he found decreases the excretion of uric acid. He thinks that uric acid is normally formed in the body by the conjugation of glycocoll and some other compound, and that when quinic acid is given, the glycocoll is diverted to form hippuric acid by conjugation with the benzoic acid, which is formed by oxidation of quinic acid. Many years before, Maly[2] and Latham[3] recommended that benzoic acid be given in gout. They stated that it would probably decrease the excretion of uric acid for this same reason. According to Weiss,[4] Blumenthal,[5]

[1] R. Burian. Ueber die oxydative und die vermeintliche synthetische Bildung von Harnsäure in Rinderleberauszug. Zeitschr. für physiol. Chem., 43, 497 (1905).

[2] R. Maly. Ueber das Verhalten der Oxybenzoesäure und Paraoxybenzoesäure in der Blutbahn. Sitzungsber der Wiener Akad. d. Wissensch. 65, 2. Abt., 39 (1872).

[3] P. Latham. Some Points on the Pathology of Rheumatism, Gout, and Diabetes. (Croonian Lectures.) Lancet (1886), 1, 626, 673, 723, 771.

[4] J. Weiss. Beiträge zur Erforschung der Bedingungen der Harnsäurebildung. Zeitschr. für physiol. Chem., 25, 393 (1898).

Ibid. Die Chinasäure als Antiarthriticum. Verhandl. der Dtsch. Gesell. der. Naturförscher und Aerzte, München (1899).

Ibid. Eine neue Methods der Behandlung der harnsäure Diathese. Berl. klin. Wochenschrift, 36, 297 (1899).

Ibid. Weitere Beiträge zur Erforschung der Bedingungen der Harnsäurebildung. Zeitschr. für physiol. Chem., 27, 216 (1899).

Ibid. Die Erfolge der Urosin Behandlung bei harnsäurer Diathese. Verhandl. des 18t Kongr. für innere Medizin, 477 (1900).

[5] Blumenthal. Ueber Sidonal, ein neues Heilmittel. Verhandl. des Vereins für innere Med. zu Berl., 19, 480 (1899–1900).

Blumenthal und Lewin. Ueber Sidonal, Chinasäures Piperazin. Therapie der Gegenwart, Neue Folge, 2, 160 (1900).

Bardet,[1] Schlayer,[2] and Lewin,[3] quinic acid decreases the excretion of uric acid, and according to Huber and Lichtenstein,[4] less uric acid is formed from the nucleins after use of quinic acid. On the other hand, Nicolaier,[5] Nicolaier and Hagenburg,[6] Lewandowski,[7] Foerster,[8] de la Camp,[9] Ulrici,[10] and Hupfer [11] have shown that quinic acid has no effect on the excretion of uric acid, and His [12] has shown that citron eating does not increase the excretion of uric acid.

If Weiss's theory were true, we should expect that benzoic and salicylic acids would decrease the excretion of uric acid. Only Ulrici,[10] who observed a very slight decrease, found this so in the case of benzoic acid. Maly,[13] Lewandowski,[7] Schreiber and Waldvogel,[14] and Nicolaier and Hagenburg [6] found that the administration of benzoic acid does not affect the excretion of uric acid. Nicolaier and Hagenburg found likewise that cinnamic acid does not influence the excretion of uric acid. In regard to salicylic acid we know that this compound even increases the excretion of uric acid.

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[1] C. Bardet. Traitement de la goutte et du rheumatisme goutteux par le sidonal ou quinate de piperazine. Bulletin général de thérapeutique, 141, 518 (1901).

[2] Schlayer. Erfahrungen über Sidonal bei Gicht. Therapie der Gegenwart., N. F. 2., 237 (1900).

[3] C. Lewin. Beiträge zum Hippursaürestoffwechsel des Menschen. Zeitschr. für klin. Med., 42, 371 (1901).

[4] Huber und Lichtenstein. Ueber Gicht und ihre Behandlung mit Chinasäure. Berl. klin. Wochenschrift, 39, 653 (1902).

[5] A. Nicolaier. Experimentelles und Klinisches über Urotropin. Zeitschr. für klin. Med., 38, 356 (1899).

Ibid. Centralblatt für Stoffwechselkrankheiten (1900).

[6] A. Nicolaier und J. Hagenburg. Ueber Chinotropin, (chinasäures Urotropin). Centralblatt für Stoffwechsel und Verdauungskrankheiten, 1, 131 (1900), and Maly's Jahresb. über die Fortschritte der Thierchemie, 30, 616 (1900).

[7] M. Lewandowski. Versuche über den Einfluss der Benzoesäure auf die Harnsäurebildung. Zeitschr. für klin. Med., 40, 202 (1900).

[8] Foerster. Versuche über die Beeinflussung der Harnsäureausscheidung mit specielle, Berucktsichtigung der Chinasäure und der chinasäuren Sälze. Inaug. Dissert., Breslau, (1900).

[9] de la Camp. Chinasäure und Gicht. München med. Wochenschrift, 48, 1203 (1901).

[10] H. Ulrici. Ueber pharmakologische Beeinflussung der Harnsäureausscheidung. Arch. für exp. Path. u. Pharmak., 46, 321 (1901).

[11] F. Hupfer. Einwirkung von Chinasäure auf Harnsäure und Hippursäureausscheidung. Zeitschr. für physiol. Chem., 37, 302 (1903).

[12] W. His. Die Ausscheidung von Harnsäure im Urin der Gichtkranken mit besonderer Berücktsichtigung der Anfallszeiten und bestimmter Behandlungsmethoden. Deutsche Arch. für klin. Medizin, 65, 156 (1900).

[13] R. Maly. Ueber das Verhalten der Oxybenzoesäure und Paroxybenzoesäure in der Blutbahn. Sitzungsber. der Wiener Akad. d. Wissenschaft., 65, 2, Abt, 39 (1872).

[14] Schreiber und Waldvogel. Beiträge zur Kenntniss der Harnsäureausscheidung unter physiologischen und pathologischen Verhältnissen. Arch. für exp. Path. u. Pharmak., 42, 69 (1899).

In spite of the fact that the evidence seems to show that quinic acid does not decrease the excretion of uric acid, and that Weiss's whole theory has been shown to be erroneous, good clinical results have been obtained in gout through the use of different quinic acid preparations by v. Leyden,[1] Goldscheider,[1] Mayer,[2] Meyer,[2] Ewald,[2] Mylius,[3] Sternfeld,[4] Salfeld,[5] v. Noorden,[6] and Huber and Lichtenstein.[7] If quinic acid is good in gout, it must be on account of some action on the metabolism that we do not at present understand.

It is interesting to note that those drugs whose use in gout has been recommended from theoretical reasons based on the supposed effect of the drug on the uric acid metabolism have been found clinically good in the treatment of gout. These drugs include the organic and inorganic alkaline bodies, urea, and the quinic acid preparations. More careful experiment has shown that the scientific theories on which the use of these drugs has been based are erroneous. This is a very peculiar coincidence. Either a peculiar combination of accidents has made us familiar with a long series of drugs which for some unknown reason are good in gout, or the methods of observation of some good clinicians are open to criticism.

ALCOHOL

According to Ries [8] and Pfeiffer,[9] alcohol drinking decreases the excretion of uric acid. Von Jaksch [10] found that alcoholic

[1] v. Leyden, and also Goldscheider. Discussion of Blumenthal's article: Ueber Sidonal ein neues Gichtmittel. Verhandl. des Vereins für innere Medizin, in Berlin, 5 Mai, 19, 480 (1899–1900).

[2] J. Mayer, E. Meyer, und Ewald. In discussion of Blumenthal's article: Ueber Sidonal, ein neues Gichtmittel. Verhandl. der Vereins für innere Medizin, Berl., 19, 480 (1899–1900).

[3] Mylius. Ueber die Einwirkung des Sidonals bei Gicht. Therapeutische Monatshefte 14, 658 (1900).

[4] H. Sternfeld. Die Chinasäure, ein neues Heilmittel gegen Gicht. München med. Wochenschrift, 48, 260 (1901).

[5] Salfeld. Zur Behandlung der Gicht mit Chinasäure. München med. Wochenschrift, 48, 633 (1901).

[6] v. Noorden. Ueber Urol. (chinasäures Harnstoff). Centralblatt für Stoffwechsel- und Verdauungskrankheiten, Sept., 1901.

[7] Huber und Lichtenstein. Ueber Gicht und ihre Behandlung mit Chinasäure. Berl. klin. Wochenschrift, 39, 653 (1902).

[8] L. Ries. Ueber den Einfluss des Alkohols auf den Stoffwechsel des Menschen. Zeitschr. für klin. Med., 2, 1 (1881).

[9] E. Pfeiffer. Die Natur und Behandlung der Gicht. Verhandl. des 8t Kongr. für innere Medizin, 166 (1889).

[10] R. von Jaksch. Der Weingeist als Heilmittel. Verhandl. des 7t Kongr. für innere Medizin, 86 (1888).

liquors decrease very slightly the excretion of uric acid in children. Weiss [1] found that cognac decreases very slightly the excretion of uric acid, and Laquer [2] that beer, wine, and whiskey have the same effect.

Chittenden,[3] and Donogány and Tibald [4] found that alcohol increases the excretion of uric acid in dogs. According to Schultz,[5] Herter,[6] and Chotzen,[7] the same is true in man. Rosenfeld [8] found that beer drinking increases the excretion of uric acid. Beer, ale, and porter contain from .002 to .006 per cent of purin bases according to Hall.[9] This would lead us to expect increased excretion of uric acid from these liquors.

Schreiber [10] and Haeser [11] could not find that alcohol has any effect on the excretion of uric acid. Herrmann [12] and Leber [13] administered malt wine, Herter and Smith [14] champagne and whiskey, and Rosemann [15] cognac, but in no case was there any increase in the excretion of uric acid.

Chittenden and Beebe [16] have experimented with whiskey, beer,

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[1] J. Weiss. Ueber den Einfluss von Alkohol und Obst auf die Harnsäurebildung. München med. Wochenschrift, 48, 1048 (1901).

[2] Laquer. Ueber die Ausscheidungsverhältnissen der Alloxurkörper im Harne von Gesunden und Kranken. Verhandl. der 14t Kongr. für innere Medizin, 33 (1896).

[3] R. Chittenden. The Influence of Alcohol on Protein Metabolism. Journ. of Physiol., 12, 220 (1891).

[4] J. Donogány und N. Tibald. Ueber den Einfluss des Alkohols auf den Eiweisszerfall im Organismus. Ungarisches Arch. für klin. Medizin, 3, 189 (1894), Maly's Jahresb. über die Fortschritte der Thierchemie, 24, 552 (1894).

[5] E. Schultz. Ueber den Einfluss der Nahrung auf die Ausscheidung der amidartigen Substanzen. Pflüger's Archiv, 45, 401 (1889).

[6] C. Herter. Some Practical Points Regarding the Excessive Excretion of Uric Acid. N. Y. Med. Journ., 58, 8 (1893).

[7] Chotzen. Zur Frage der Fleischersatzmittel. Inaug. Dissert., Breslau (1897).

[8] G. Rosenfeld. Des Einfluss des Alkohols auf den Organismus. Wiesbaden (1901). Centralblatt für innere Medizin, 21, 47 (1901).

[9] J. Hall. Vegetabilische Nahrung und Getränke bei Gicht und Nephritis. Berl. klin. Wochenschrift, 40, 868 (1903).

[10] Schreiber. Ueber die Harnsäure, 38, Stuttgart (1899).

[11] H. Haeser. Der Einfluss des Alkohols auf die Harnsäureausscheidung. Inaug. Dissert., Greifswald (1901).

[12] A. Herrmann. Ueber die Abhängigkeit der Harnsäureausscheidung von Nährungs- und Genussmitteln mit Rucksicht auf die Gicht. Deutsche Arch. für klin. Medizin, 43, 273 (1888).

[13] H. Leber. Zur Physiologie und Pathologie der Harnsäureausscheidung beim Menschen Berl. klin. Wochenschrift, 34, 956 (1897).

[14] Herter and E. Smith. Observations on the Excretion of Uric Acid in Health and Disease. N. Y. Med. Journ., 55, 617 (1892).

[15] R. Rosemann. Ueber den Einfluss des Alkohols auf die Harnsäureausscheidung. Deutsche med. Wochenschrift, 27, 531 (1901).

[16] R. Chittenden and S. Beebe. The Effect of Alcohol and Alcoholic Fluids upon the Excretion of Uric Acid in Man. Proc. of the Am. Physiol. Soc. 1903, Am. Journ. Physiol., 9, 1 (1903).

and wine. They administered these beverages to the extent of from 70 to 80 cubic centimeters of absolute alcohol per day. Whiskey had scarcely any effect on the uric acid excretion. After wine and beer there was a slightly increased excretion of uric acid.

According to Beebe,[1] alcohol increases the excretion of uric acid and the purin bodies. It seems to prevent the complete oxidation of the purin bodies of the food, for when it is taken without food it does not increase the excretion of uric acid, and, further, the maximum excretion of uric acid after taking alcohol and food occurs at the same time as when the alcohol is not taken.

According to Schittenhelm,[2] the purin bodies in the feces are decreased in alcoholic stools.

The trouble with most of the experimental work concerning the effect of alcohol and other drugs on the excretion of uric acid is that the diet has not been so regulated as to keep the amount of uric acid excreted constant from day to day. The greater part of the work has not been done recently enough to take advantage of our present knowledge concerning the metabolism of uric acid. We now know enough about the effect of different foodstuffs on the excretion of uric acid to be able to keep the excretion of uric acid fairly constant by regulating the diet.

According to Neumayer [3] beer and white wine increase the so-called "free" uric acid, which is given up to a uric acid filter. Red wine and pure alcohol have no effect. Rosenfeld [4] and Glaser,[5] too, found that alcohol causes a large precipitate of uric acid in the urine.

COLCHICUM

Colchicum is a drug which has long been used as a therapeutic agent in gout. Only His,[6] Ransome,[7] and Liebreich [8] have studied its effect on the excretion of uric acid in recent times.

[1] S. Beebe. The effect of alcohol and alcoholic fluids upon the excretion of uric acid in man. Am. Journ. of Physiol., 12, 13 (1904).

[2] A. Schittenhelm. Die Purinkörper der Fäces nebst untersuchungen über die Purinbasen der Darmwand, der Galle und des Pankreassaftes. Arch. für klin. Medizin, 81, 423 (1904).

[3] H. Neumayer. Discussion in d. Versamml. des 14t Kongr. für innere Medizin (1896), 14, 24, and Ueber die Therapie des harnsäuren Diathese. Verhandl. des aerztliches vereins in München 9 März, 1898, und Deutsche med. Wochenschrift, 24, vereins Beilage 60 (1898).

[4] R. Rosenfeld. Der Einfluss des Alkohols auf der Organismus. Wiesbaden, 1901.

[5] Glaser. Ueber den Einfluss alkoholischer Getränke auf das Harnsediment der normalen Menschen. Deutsche med. Wochenschrift, 17, 1193 (1891).

[6] W. His. Untersuchungen an Gichtkranken. Wien. med. Blätter, 19, 291 (1896).

[7] C. Ransome. Colchicum in the Treatment of Gout. Medical News, 82, 1105 (1903).

[8] Liebreich. Artikel — Colchicum— in Encyklopädie der Therapie (1896), 1, 757.

His and Ransome could not find that it has any effect. According to Liebreich, the action of colchicum on the excretion of uric acid depends somewhat on the condition of the kidneys. Among older experimenters, Noël-Paton [1] found increased uric acid in dogs, and Mairet and Combemale [2] increased uric acid in man after colchicum. Graves and Bresster [3] and Lecorché,[4] on the other hand, found decreased excretion of uric acid. Moss [5] could not find that colchicum has any effect.

ANTIPYRIN, ANTIFEBRIN, AND PHENACETIN

The evidence in the case of antipyrin is contradictory. According to Robin [6] and Levison,[7] the administration of antipyrin causes an increased excretion of uric acid in man. Kumagawa [8] found the same result in dogs. Chittenden [9] and Horbaczewski,[10] on the other hand, observed a slightly decreased excretion of uric acid in man after antipyrin. Umbach,[11] Bohland,[12] Tanszk and Vas,[13] and Stroux [14] could not observe that this drug has any effect on uric acid excretion.

Chittenden and Taylor [15] observed a decrease in the excretion

[1] D. Noël-Paton. On the Nature of the Relationship of Urea Formation to Bile Secretion. Journ. of Anat. and Physiol., 20, 114, and 265 (1886).

[2] A. Mairet et Combemale. Recherches sur le mode d'action de la colchicine prise à dose thérapeutique et la mécanisme de cette action. Comptes rendus, 104, 515 (1887).

[3] Graves und Bresster. Klinische Beobachtungen. Leipzig (1847).

[4] Lecorché. Traité de la Goutte, Paris (1884).

[5] Moss. On the Action of Potash, Soda, Lithia, Lead, Opium, and Colchicum on the Urine. Am. Journ. of Med. Sciences, 41, 384 (1861).

[6] A. Robin. Wirkung des Antipyrins auf die Ernahrung. Bull. de l'acad. de méd. (1887), 49; Maly's Jahresb. über die Fortschritte der Thierchemie, 18, 267 (1888).

[7] C. Levison. Ueber den Einfluss einiger Medicamente auf Harnsäureausscheidung und Leukocytenzahl. Inaug. Dissert., Düsseldorf (1897).

[8] M. Kumagawa. Ueber die Wirkung einiger antipyretischer Mittel auf den Eiweissumsatz im Organismus. Virchow's Archiv, 113, 134 (1888).

[9] R. Chittenden. Ueber den Einfluss von Urethan, Antipyrin, und Antifebrin auf den Eiweissumsatz. Zeitschr. für Biologie, 25, 496 (1889).

[10] Horbaczewski. Beiträge zur Kenntniss der Bildung der Harnsäure und der Xanthinbasen, sowie der Entstehung der Leukocyten im Säugethierorganismus. Monatshefte für Chemie, 12, 221 (1891).

[11] C. Umbach. Ueber den Einfluss des Antipyrins auf die Stickstoffausscheidung. Arch. für exp. Path. u. Pharm., 21, 161 (1886).

[12] K. Bohland. Ueber den Einfluss einiger Arzneimittel auf die Bildung und Ausscheidung der Harnsäure. München med. Wochenschrift, 46, 505 (1899).

[13] F. Tanszk und B. Vas. Ueber den Einfluss einiger Antipyretica auf den Stoffwechsel. Ungar. Arch. für Med., 1, 204 (1892), Maly's Jahresb. über die Fortschritte der Thierchemie, 22, 438 (1892).

[14] H. Stroux. Ueber die Beeinflussung der Harnsäure durch verscheidene Arzneimittel. Inaug. Dissert., Bonn (1896).

[15] Chittenden and Taylor. The Influence of Urethane, Paraldehyde, Antipyrine, and Antifebrin on the Proteid Metabolism. Studies from the Laboratory of Physiological Chemistry, Yale (1887–88).

of uric acid after antifebrin. Tanzsk and Vas [1] could not find that it has any effect.

According to Stroux [2] and Bohland,[3] phenacetin has very little influence on the excretion of uric acid. According to Levison,[4] this drug increases the excretion of uric acid.

QUININE

Only Richter [5] observed no effect of quinine on the excretion of uric acid. Decreased excretion of uric acid after administration of quinine has been observed in man by Ranke,[6] Binz,[7] Kerner,[8] Chittenden and Whitehouse,[9] Prior,[10] Levison,[4] Horbaczewski,[11] Stroux,[2] and Bohland [3]; in the dog by Kumagawa,[12] and in the cat by Mendel and Brown.[13] According to Zagari and Pace,[14] quinine increases the excretion of uric acid in man.

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[1] F. Tanzsk und B. Vas. Ueber den Einfluss einiger Antipyretica auf den Stoffwechsel. Ungar. Arch. für Med., 1, 204 (1892), Maly's Jahresb. über die Fortschritte der Thierchemie, 22, 438 (1892).

[2] H. Stroux. Ueber die Beeinflussung der Harnsäure durch verscheidene Arzneimittel. Inaug. Dissert., Bonn (1896).

[3] K. Bohland. Ueber den Einfluss einiger Arzneimittel auf die Bildung und Ausscheidung der Harnsäure. München med. Wochenschrift, 46, 506 (1899).

[4] C. Levison. Ueber den Einfluss einiger Medicamente auf Harnsäureausscheidung und Leukocytenzahl. Inaug. Dissert., Düsseldorf (1897).

[5] P. Richter. Ueber Harnsäureausscheidung und Leukocyten. Zeitschr. für klin. Med., 27, 290 (1895).

[6] H. Ranke. Beobachtungen und Versuche über die Ausscheidung der Harnsäure beim Menschen. München (1858).

[7] C. Binz. Pharmakologische Studien über Chinin. Virchow's Archiv, 46, 67, and 129 (1869).

[8] G. Kerner. Beiträge zur Kenntniss der Chininresorption. Pflüger's Archiv, 3, 93 (1870).

[9] Chittenden and Whitehouse. Influence of Cinchonidin Sulphate on Metabolism. Studies from the Laboratory of Physiological Chemistry, Sheffield Scientific School, Yale College (1884–85).

[10] Prior. Ueber den Einfluss des chinin auf den Stoffwechsel des gesunden Organismus. Pfluger's Archiv, 34, 237 (1884).

[11] Horbaczewski. Beiträge zur Kenntniss der Bildung der Harnsäure und der Xanthinbasen, sowie der Entstehung der Leukocyten im Säugethierorganismus. Monatshefte für Chemie, 12, 221 (1891).

[12] M. Kumagawa. Ueber die Wirkung einiger antipyretischen Mittel auf den Eiweissumsatz in Organismus. Virchow's Archiv, 13, 134 (1888).

[13] L. Mendel and E. Brown. Observations on the Nitrogenous Metabolism of the Cat, Especially on the Excretion of Uric Acid and Allantoin. Am. Journ. of Physiol., 3, 261 (1901).

[14] G. Zagari e D. Pace. La genesi dell' acido urico e la gotta in riguardo alla patogenesi e all' indirizzo terapeutico. Napoli, 1897. Centralblatt für innere Medizin, 19, 816 (1898).

TANNIC ACID AND TANNIN

According to Levison,[1] Dolff,[2] and Bohland,[3] the administration of tannic acid causes a decrease in the excretion of uric acid. The same is true of tannin, according to Levison [4] and Sabrezés and Frézal.[5] Neither Weiss [6] nor Ulrici [7] could find that tannin has any influence on the quantity of uric acid excreted. Tannic acid has no effect on the excretion of uric acid in cats, according to Mendel and Brown.[8]

LEAD

In view of the fact that lead poisoning sometimes seems to lead to gouty changes, it is rather surprising that but few attempts have been made to study the effect of lead poisoning on the excretion of uric acid. According to Garrod,[9] who used the inaccurate Heinz method of determination, there is a very slight decrease in the excretion of uric acid in lead poisoning. This was confirmed by Bouchard [10] and Gaucher.[11] Surmont and Brunelle [12] state that when the lead poisoning lasts but a short time, there is a decreased excretion of uric acid; when the lead poisoning extends over a long period, the excretion of uric acid is increased. Luthje [13] could not find that there is any change in the excretion of uric acid in lead poisoning in dogs.

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[1] C. Levison. Ueber den Einfluss einiger Medicamente auf Harnsäureausscheidung und Leukocytenzahl. Inaug. Dissert., Bonn (1897).

[2] F. Dolff. Ueber den Einfluss von nucleinreicher Nahrung und Acidum tannicum auf den Harnsäureausscheidung beim Menschen. Inaug. Dissert., Bonn (1898).

[3] K. Bohland. Ueber den Einfluss Arzneimittel auf die Bildung und Ausscheidung der Harnsäure. München med. Wochenschrift, 46, 505 (1899).

[4] F. Levison. Zur Lehre von der Pathogenese der Gicht. Zeitschr. für klin. Med., 26, 293 (1894).

[5] J. Sabrezés et M. Frézal. Action du tannin sur la diurese. Journ. de phys. et de path. général, 1, 221 (1899).

[6] J. Weiss. Weitere Beiträge zur Erforschung der Bedingungen der Harnsäure-Bildung. Zeitschr. für physiol. Chem., 27, 216 (1899).

[7] H. Ulrici. Ueber pharmakologische Beeinflussung der Harnsäureausscheidung. Arch. für exp. Path. u. Pharm., 46, 321 (1901).

[8] L. Mendel and E. Brown. Observations on the Nitrogenous Metabolism of the Cat, Especially on the Excretion of Uric Acid and Allantoin. Am. Journ. of Physiol., 3, 261 (1900).

[9] A. Garrod. The Nature and Treatment of Gout.

[10] Bouchard. Leçons sur les maladies par ralentissement de la nutrition. Paris (1890).

[11] Gaucher. Les troubles de la nutrition dans l'intoxication saturnine. Révue de médecine (1881).

[12] Surmont et Brunelle. Recherches sur l'élimination de l'azote urinaire au cours et dans la convalescence de la colique saturnine. Arch. gén. de méd. (1894).

[13] C. Luthje. Ueber Bleigicht. Zeitschr. für klin. Med., 29, 266 (1896).

OTHER DRUGS

Pöhl [1] states that spermin decreases the excretion of uric acid, and Richter [2] that it has no effect. According to Zagari and Pace,[3] spermin increases the excretion of uric acid.

Umbach [4] and Noël-Paton [5] found a slight decrease in the excretion of uric acid after calcium sulphide.

According to Eckart,[6] Kollmann,[7] and Sticker,[8] the inhalation of oxygen decreases the excretion of uric acid. According to Krafft [9] and Honigmann,[10] it has no effect.

Mares,[11] and Kühnau and Weiss [12] observed a slight increase in the excretion of uric acid after pilocarpin.

After urotropin, Rosenfeld and Orgler [13] found the excretion of uric acid decreased, while His [14] and Bain [15] found it unchanged.

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[1] A. Pöhl. Einwirkung des Spermins auf den Stoffumsatz bei Autointoxicationen im Allgemeinen und bei harnsäurer Diathese im Speciellen. Zeitschr. für klin. Med., 26, 135 (1894).

[2] P. Richter. Ueber Harnsäureausscheidung und Leukocyten. Zeitschr. für klin. Med., 27, 290 (1895).

[3] G. Zagari e D. Pace. La genesi dell' acido urico e la gotta in riguardo alla patogenesi e all' indirizzo terapeutico. Napoli, 1897. Centralblatt für innere Medizin, 19, 816 (1898).

[4] C. Umbach. Ueber den Einfluss des Antipyrins auf die Stickstoffausscheidung. Arch. für exp. Path. u. Pharm, 21, 161 (1886).

[5] D. Noël-Paton. On the Nature of the Relationship of Urea Formation to Bile Secretion. Journ. Anat. and Physiol., 20, 114, and 265 (1886).

[6] Eckart. Die acute Gicht und ihre Behandlung. München (1864).

[7] Kollmann. München. ärztl. Intelligenzblatt, 22, (1869).

[8] G. Sticker. Beiträge zur Pathologie und Therapie der Leukämie. Zeitschr. für klin. Med., 14, 80 (1888), *and*

Der Bostock's Sommerkatarrh (Heufieber), in Nothnagel's Handbuch (1896), 4, 1, 85.

[9] Krafft. Chemische Untersuchungen über den Einfluss von Sauerstoff Inhalationen auf die Stickstoffprodukte im Harn. Rev. méd. de la suisse, Rom., 4, 295 (1890). Fortschritte der Med., 7, 776 (1890).

[10] G. Honigmann. Beiträge zur Kenntniss der Wirkung von Sauerstoffeinathmungen auf den Organismus. Zeitschr. für klin. Med., 19, 270 (1891).

[11] F. Mares. Sur l'origine de l'acide urique chez l'homme. Archives slaves de biologie, 36, 307, and Centralblatt für innere Medizin, 26, 2 (1888).

[12] W. Kühnau und F. Weiss. Weitere Mittheilungen zur Kenntniss der Harnsäureausscheidung bei Leukocytose und Hypoleukocytose sowie zur Pathologie der Leukämie. Zeitschr. für klin. Med., 32, 482 (1897).

[13] Rosenfeld und Orgler. Zur Behandlung der harnsäuren Diathese. Centralblatt für innere Medizin, 17, 42 (1896), and

G. Rosenfeld. Grundzuge der Behandlung der harnsäuren Diathese. Verhandl. des 14t Kongr. für innere Medizin, 318 (1896).

[14] W. His. Die Ausscheidung von Harnsäure im Urin der Gichtkranken mit besonderer Berucksichtigung der Anfallzeiten und bestimmter Behandlungsmethoden. Deutsche Arch. für klin. Medizin, 65, 156 (1900).

[15] W. Bain. The Influence of Some Modern Drugs on Metabolism in Gout. Brit. Med. Journ., 1, 243 (1903).

According to Horbaczewski,[1] Stroux,[2] Bohland,[3] and Levison,[4] atropin decreases the excretion of uric acid.

Sticker[5] found that arsenic, and Ritter[6] that N_2O decreases slightly the excretion of uric acid.

Stroux,[2] Bohland,[3] and Levison[4] could not find that campheric acid has any effect on the uric acid excretion.

According to Munzer and Palmer,[7] the excretion of uric acid is increased in carbon monoxide poisoning.

Robin[8] found decreased excretion of uric acid after thallium.

Mortessier[9] could not find that kola nut has any effect on the excretion of uric acid.

The replacement of NaCl by KCl in the food does not influence the excretion of uric acid, according to Herrmann.[10]

BATHS

After a hot bath, Laquer[11] found the excretion of uric acid increased. Formanck[12] noticed a slight increase in the excretion of uric acid after hot baths. He found also that a single cold bath has no effect, but that two long cold baths per day increase the excretion of uric acid. According to

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[1] Horbaczewski. Beiträge zur Kenntniss der Bildung der Harnsäure und der Xanthinbasen, sowie der Entstehung der Leukocyten im Säugethierorganismus. Monatshefte für Chemie, 17, 221 (1891).

[2] H. Stroux. Ueber die Beeinflussung der Harnsäure durch verschiedene Arzneimittel. Inaug. Dissert., Bonn (1896).

[3] K. Bohland. Ueber den Einfluss einiger Arzneimittel auf die Bildung und Ausscheidung der Harnsäure. München med. Wochenschrift, 46, 505 (1899).

[4] C. Levison. Ueber den Einfluss einiger Medicamente auf Harnsäureausscheidung und Leukocytenzahl. Inaug. Dissert., Düsseldorf (1897).

[5] G. Sticker. Beiträge zur Pathologie und Therapie der Leukämie. Zeitschr. für klin. Med., 14, 80 (1888).

[6] Ritter. Mode d'action du protoxyde d'azote. Revue médical de l'Est, 1, 41 (1874), Maly's Jahresb. über die Fortschritte der Thierchemie, 4, 191 (1874).

[7] E. Munzer und P. Palmer. Ueber den Stoffwechsel des Menschen bei Kohlendunst- und Nitrobenzolvergiftung. Zeitschr. für Heilk., 15, 1 (1894).

[8] A. Robin. Physiologische Wirkung der Thallium, seine therapeutischen contraindicationen. Arch. d. Physiol., 21, 667 (1890), Maly's Jahresb. über die Fortschritte der Thierchemie, 20, 347 (1890).

[9] J. Mortessier. Influence du travail musculaire sur l'élimination de la créatinine. Compt. rend. soc. Biol., 43, 573 (1891), Maly's Jahresb. über die Fortschritte der Thierchemie, 21, 182 (1891).

[10] A. Herrmann. Ueber die Abhangigkeit der Harnsäureausscheidung von Nahrungs- und Genussmitteln mit Rücksicht auf die Gicht. Deutsche Arch. für klin. Medizin, 43, 273 (1888).

[11] B. Laquer. Ueber die Ausscheidungsverhältnisse der Alloxurkörper im Harne von Gesunden und Kranken. Verhandl. des 14t Kongr. für innere Medizin, 333 (1896).

[12] Formanck. Ueber den Einfluss kalter Bäder auf die Stickstoff- und Harnsäureausscheidung beim Menschen. Zeitschr. für physiol. Chem., 19, 271 (1891).

Ebstein,[1] baths do not affect the excretion of uric acid. Makowiecki,[2] who found a slightly decreased excretion of uric acid after hot baths, used the inaccurate Haycraft method for determining uric acid.

It can be seen that the results of experiments on the effect of drugs on the excretion of uric acid are often contradictory. In a good deal of the work inaccurate methods for the determination of uric acid were used. In most of the work the diet was not carefully regulated. We have not criticized the experiments individually, since the effect of drugs on the size of the uric acid excretion cannot be said to mean much at the present time. There is no drug which we can say either decreases the formation of uric acid, furthers its excretion, hastens its further oxidation, or increases its solubility in the blood or tissue fluids.

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[1] W. Ebstein. The Regimen to be Adopted in Cases of Gout. English transl. by J. Scott (1885).

[2] N. Makowiecki. Zur Frage der Einwirkung desrussischen Schwitzba des auf Stickstoffumsatz und Fettassimilation und auf die Assimilation der stickstoffhaltigen Bestandtheile der Nahrung bei Gesunden. Inaug. Dissert., Petersburg (1888); Maly's Jahresb. über die Fortschritte die Thierchemie, 18, 289 (1888).

III. Pathology

In the section on uric acid in pathological conditions, we shall consider chiefly gout, although for completeness, a brief chapter on uric acid in other pathological conditions will be added. Certain authors have maintained that when sodium acid urate precipitates and forms concretions in the tissues for any reason, these concretions cause either mechanical or chemical irritation or necrosis. Others have stated that the purin bases, the antecedents of uric acid, produce toxic symptoms. The truth of these facts has been disputed. We shall, therefore, precede our treatment of gout itself by a discussion of the action of uric acid and the purin bases in the body.

Toxicology of Uric Acid and the Purins

The action of only hypoxanthin, xanthin, guanin, adenin, uric acid, and urates is of interest to us. Caffein and theobromin are known to have decided action in the body, but since they affect the uric acid metabolism little if any, they are of no interest from our standpoint.

General Action

Filehne [1] obtained tetanus in frogs after injection of hypoxanthin, and tetanus followed by cardiac arrest after xanthin. According to Paschkis and Pal,[2] injections of seven to ten milligrams of xanthin caused increased irritability in the muscles of frogs. This work was confirmed by Baldi,[3] who found that injections into frogs of 20 milligrams of xanthin dissolved in Na_2CO_3 brings about tetanus, and that smaller doses cause increased reflex irritability. Gautier [4] obtained similar results after injection of hypoxanthin into guinea pigs.

[1] E. Filehne. Ueber einige Wirkungen des Xanthins. Arch. für Anat. und Physiol., 72 (1886).

[2] Paschkis und Pal. Wien. med. Jahrb. (1886), 611.

[3] Baldi. La Terapia Moderna, No. 12 (1891).

[4] A. Gautier. Les Toxines, 1, 264 (1896).

Schmiedeberg [1] observed increased reflex irritability of muscles in pigs after injection of xanthin, and increased cerebral irritability and tetanus after injection of hypoxanthin dissolved in Na_2CO_3. This author found that practically all the members of the purin group with which he experimented bring about increased reflex irritability, and therefore attributed this action to the purin nucleus itself. Differences in the intensity of the action of different members of the group, he suggested, might be due to differences in solubility or rates of absorption. Uric acid itself seemed to be inactive in frogs.

According to Croftan,[2] injection of xanthin or hypoxanthin into rabbits causes increased blood pressure and cardiac hypertrophy.

Hall [3] could not find that hypoxanthin increases the blood pressure of rabbits. He gave small doses of hypoxanthin daily for fifty days, and found the blood pressure very constant. This author maintains that the blood pressure in Croftan's experiments was normal after the hypoxanthin injections, and that Croftan took too low values for the normal blood pressure.

According to Freudweiler,[4] hypoxanthin and xanthin are toxic when injected into rabbits.

Guanin, up to doses of 100 milligrams, is inactive in frogs, according to Filehne.[5]

According to Paschkis and Pal,[6] and Rachford,[7] paraxanthin is toxic and causes migraine, epilepsy, and certain other diseases.

Putnam and Pfaff [8] showed that Rachford used not paraxanthin, but a mixture of paraxanthin and ammonium salts, and that even this solution is not toxic in mice.

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[1] O. Schmiedeberg. Vergleichende Untersuchungen über die pharmakologischen Wirkungen einiger Purinderivate. Ber. der Dtsch. chem. Gesell., 34, 2550 (1901).

[2] A. Croftan. Rôle of Alloxuric Bases in the Production of the Cardio-Vascular Changes of Nephritis. Am. Journ. of Med. Sciences, 120, 592 (1900).

[3] I. Hall. The Purin Bodies of Foodstuffs. Manchester, Eng. (1902), also I. Hall. Metabolism in Gout and the Need for Combined Investigation. Practitioner, 71, 61 (1903).

Ibid. Beiträge zur Kenntniss der Wirkung der Purinsubstanzen. Virchow's Archiv, 174, 359 (1903).

[4] M. Freudweiler. Experimentelle Untersuchungen über die Entstehung der Gichtknoten. Deutsche Arch. für klin. Medizin, 68, 155 (1900).

[5] W. Filehne. Ueber einiger Wirkungen des Xanthins. Arch. f. Anat. u. Physiol., 72 (1886).

[6] Paschkis und Pal. Wien. med. Jahrb. (1886), 611.

[7] Rachford from Kolisch. Ueber Wesen und Behandlung der uratischen Diathese. Stuttgart (1895).

[8] J. Putnam and F. Pfaff. Disproof of Paraxanthin Poisoning Theory. Journ. of Boston Society of Medical Sciences, 3, 255 (1898).

Direct experiments with uric acid and urates have not shown that these bodies bring about general toxic symptoms. Filehne [1] and Schmiedeberg [2] found uric acid inactive in frogs. Filehne administered as much as 100 milligrams. Croftan [3] fed uric acid to dogs, and gave them injections of it for long periods without producing toxic symptoms.

According to Stadthagen,[4] a large dose of sodium acid urate caused toxic symptoms in a leukemic patient. This has not been confirmed. The symptoms might well be due to other causes. The same may be said concerning the headache observed by Hall [5] after taking uric acid in the food. Haig's [6] statement that excess of uric acid in the blood causes irritation of the vasomotor nerves, by means of which the blood pressure is raised in the arteries and smaller blood vessels giving rise to various symptoms, is a theory for which there is no proof.

According to Virchow,[7] urine rich in uric acid causes inflammation of the bladder. This has not been confirmed.

Structural Changes Due to Purin Bodies

EFFECT OF PURIN BASES

According to Gaucher,[8] injection of xanthin and paraxanthin into guinea pigs for a few weeks caused kidney lesions similar to those found after mercury and lead poisoning. Kolisch [9] found similar lesions in rabbits after injection of hypoxanthin for a month. Croftan [10] gave small injections of xanthin and hypoxanthin to rabbits for a long period, and found granular

[1] W. Filehne. Ueber einige Wirkungen des Xanthins. Arch. für Anat. u. Physiol., 72 (1886).

[2] O. Schmiedeberg. Vergleichende Untersuchungen über die pharmakologischen Wirkung einier Purinderivate. Ber. der Dtsch. chem. Gesell., 34, 2550 (1901).

[3] A. Croftan. An Investigation into the Cause of So-called Uric Acid Lesions and Rational Therapeutics of the Uratic Diathesis. N. Y. Med. Journ., 72, 221 (1900).

[4] M. Stadthagen. Ueber das Vorkommen der Harnsäure in verschiedenen tierischen Organen, ihr Verhalten bei Leukämie, und die Frage ihrer Entstehung aus den Stickstoffbasen. Virchow's Archiv, 109, 390 (1887).

[5] I. Hall. The Purin Bodies of Foodstuffs. Manchester, Eng. (1902).

[6] A. Haig. Uric Acid as a Factor in the Cause of Disease. 3d ed., Phila. (1896).

[7] R. Virchow. Ueber Nephritis arthritica. Berl. klin. Wochenschrift, 21, 1 (1884).

[8] Gaucher. Pathogénie de néphrite. Thése, Paris (1886), and Recherches expérimentelles sur la pathogénie des néphritis par auto-intoxication. Révue de Med., 8, 885 (1888).

[9] R. Kolisch. Ueber Wesen und Behandlung der uratischen Diathese. Stuttgart (1895).

[10] A. Croftan. An Investigation into the Cause of So-called Uric Acid Lesions and Rational Therapeutics of the Uratic Diathesis. N. Y. Med. Journ., 72, 221 (1900), also *Ibid.* Rôle of Alloxuric Bases in the Production of the Cardio-Vascular Changes of Nephritis. Am. Journ. of Med. Sciences, 120, 592 (1900).

degeneration of the epithelial cells lining the tubuli contorti, a proliferation of the endothelium of the intertubular capillaries, and albumin in the urine. Hall [1] found degenerative changes in the kidneys and liver of rabbits after small daily doses of hypoxanthin and guanin for fifty days. The results may not, however, be the same in man as in rabbits.

Minkowski [2] observed that adenin feeding brought about pathological changes in the kidneys of rabbits. His statement that the adenin causes the formation of uric acid concretions in the kidney is probably erroneous. In rats, Nicolaier [3] found similar concretions in the kidneys after adenin feeding, but these concretions consisted of 6-amino-2-8-dioxypurin, an oxidation product of adenin. According to Hager,[4] Carbone and Generali found that injections of adenin hydrochloride cause necrosis and inflammation. Hager does not give details concerning the kind of animal used and the place of inflammation.

EFFECT OF URIC ACID

In Birds

Physiologists have never been able to agree in their views concerning the effect of uric acid on the organism. To this fact is due in part the number of different theories of gout. The question has been studied experimentally in a number of different ways.

Ebstein [5] found after injection of potassium chromate into cocks that concretions of sodium urate appear in the kidneys. According to Ebstein, the tissue was found to be necrosed at all

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[1] I. Hall. Metabolism in Gout and the Need for Combined Investigation. Practitioner, 71, 61 (1903).

Ibid. Beiträge zur Kenntniss der Wirkung der Purinsubstanzen. Virchow's Archiv, 174, 359 (1903).

[2] O. Minkowski. Untersuchungen zur Physiologie und Pathologie der Harnsäure bei Säugethieren. Arch. für exp. Path. u. Pharm., 41, 375 (1898), also

Ibid. Ueber Stoffwechselprodukte nach Thymusfütterung. Centralblatt für innere Medizin, 19, 500 (1898).

[3] W. Nicolaier. Ueber die Umwandlung des Adenins im thierischen Organismus. Zeitschr. für klin. Medizin, 45, 359 (1902).

[4] Carbone and Generali. July Meeting of the Turin Medical Academy, according to O. Hager. Zur Pathogénie der Gicht. München. med. Wochenschrift, 47, 1101 (1900).

[5] W. Ebstein. Ueber den gichtischen Prozess. Verhandl. des 2t Kongr. für innere Medizin (1882), p. 79, also

Ibid. The Regimen to be Adopted in Cases of Gout. Transl. by Scott. London (1885), and

Ibid. La goutte, sa nature et son traitement. Transl. by E. Chambard. Paris (1887).

places where the concretions appeared. In many places the necrosed patches extended beyond the limits of the concretions. On account of these facts, Ebstein came to the conclusion that the necrosis precedes the formation of the concretions, and is caused by the urates in solution. A free acid is generated by the necrosed tissue, and this acid causes precipitation of the acid urate, according to this author. He stated further that in gout there is a necrosis where the concretions are found, and that this necrosis is of the same character as that found in the kidneys of birds after chromate injections.

Schreiber and Zaudy [1] repeated the work of Ebstein, and came to the conclusion, in agreement with this author, that tissue necrosis precedes the deposition of the urates. Ebstein still maintained this vein in a recent article.[2]

v. Kossa [3] states that oxalic acid, phenol, cane sugar, dextrose, and other substances, as well as potassium chromate, cause necrosis and formation of urate concretions in the kidney, liver, spleen, peritoneum, and in other parts of birds. Kionka [4] brought about a gouty condition in hens by feeding them exclusively on meat for a long period. He states that the condition brought about is the same as that obtained by Ebstein after potassium chromate injections. Neither Kionka nor von Kossa investigated the tissue changes very carefully, nor did they search for urates in unchanged tissue. Their results, therefore, cannot be taken as confirmation of Ebstein's view that urates deposit only in necrosed, dead tissue.

Likhatscheff,[5] on the other hand, who brought about the deposition of urates in hens by tying the ureters, found urates deposited

[1] E. Schreiber und Zaudy. Ueber die bei Vögeln künstlich zu erzeugenden Harnsäureablagerungen. Pflüger's Archiv, 79, 53 (1900).

[2] W. Ebstein. Gicht. In Ebstein und Schwalbe's Handbuch der praktischen Medizin. Bd. III, Th. 2 (1901), Stuttgart.

[3] J. von Kossa. Künstlich Erzeugung der Gicht durch Gifte. Arch. internat. de Pharmacodynamie, 5, 97 (1898), also

Ibid. Beitrag zur Wirkung der Zuckerarten. Pflüger's Archiv, 75, 310 (1899).

[4] H. Kionka. Zur Kenntniss des Stoffwechsels fleischgefütterter Hühner. Arch. für Pharmacodynamie, 7, 55 (1900), also

Ibid. Entstehung und Wesen der "Vogelgicht" und ihre Beziehung zur Arthritis urica des Menschen. Arch. für exp. Path. u. Pharm., 44, 186 (1900), also

Ibid. Einfluss des Kalkes auf das physiologische Verhalten gichtkranker Hühner. Arch. für exp. Path. u. Pharm., 44, 207 (1900).

[5] A. Likhatscheff. Experimentelle Untersuchungen über die Folgen der Ureterunterbindung bei Huhnern mit besonderer Berücksichtigung der nachfolgenden Uratablagerung. Ziegler's Beiträge zur pathologischen Anatomie und allgemein Pathologie, 20, 102 (1896).

in healthy tissue. This discovery has been confirmed by Freudweiler.[1]

Riehl [2] likewise found urates in unchanged, healthy tissue. According to this author, Ebstein's results are due to his manner of preparing sections for examination. When the sections are brought into water a little of the urate at the periphery of the concretions dissolves. This leaves a slight space between the urates and the healthy tissue. It was this space, according to Riehl, that led Ebstein to believe that there is a necrosis. Riehl prepared sections for examination without bringing them into contact with water, and found that the urate crystals extend into the unchanged tissue.

Freudweiler [1] caused tissue necrosis in birds by burning. He then tied the ureters and brought about the deposition of urates. Urate crystals were not found in the burned tissue. Freudweiler concluded that necrosed tissue does not attract urates.

On account of the different position which uric acid holds in the metabolism of birds from that which it holds in mammals, we cannot draw conclusions concerning gout from results obtained by artificially disturbing the metabolism of uric acid in birds. Further, Freudweiler [1] has called attention to the fact that in gout the urates are found chiefly in the joints and cartilage rather than in the internal organs, and that in birds with tied ureters, or suffering from chromate poisoning, the urates are found in the internal organs and in the serous tissue, while the joints are generally quite free from urates. Zaudy [3] states that the urates in the joints of birds with tied ureters are found only on the surface of the cartilage, while in gout the urates are found in the substance of the articular cartilage. It will be well to remember, however, that even in birds necrosis does not precede the deposition of urates, when for any reason there is such a deposition in the tissues.

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[1] M. Freudweiler. Experimentelle Untersuchungen über die Entstehung der Gichtknoten. Deutsche Arch. für klin. Medizin, 68, 155 (1900).

[2] G. Riehl. Zur Anatomie der Gicht. Wien. klin. Wochenschrift, 10, 761 (1897), also

Ibid. Ueber die Anatomie der Gichtknoten. Vortrag. gehalten in der Leipziger medicinischer Gesellschaft., 9 Febr., 1897; Schmidt's Jahrb., 253, 271 (1897).

[3] Zaudy. Bemerkungen zur der Arbeit von His: Schicksal und Wirkung des säuren harnsäuren Natrons in Bauch und Gelenkhöhle des Kaninchens. Deutsche Arch. für klin. Medizin, 67, 377 (1900).

In Mammals

As a result of his experiments on birds, Ebstein came to the conclusion that urates in solution are toxic, and attempted to confirm his view by experiments on mammals. He found that by injection of a solution of uric acid in Na_2HPO_4 into the cornea of a rabbit, inflammation and obscurity can be brought about. With Na_2HPO_4 alone, or with xanthin, guanin, creatin, or hippuric acid, he could not get toxic action.[1] After intravenous, subcutaneous, and intraperitoneal injections of urate into rabbits, crystals of uric acid were found in the kidneys.[1, 2]

Heidenhain and Neisser [3] had previously observed the presence of urate crystals in the kidneys of rabbits after intravenous injection of urates. Freudweiler [4] injected uric acid in suspension, and also sodium acid urate solution into rabbits and into men, and concretions of uric acid were obtained. The uric acid and urates did not act merely like a foreign body, $CaCO_3$ for example. The inflammation came on sooner, was more intense, and lasted longer in the case of the uric acid than in the case of $CaCO_3$. Uric acid and sodium acid urate are, therefore, toxic, according to this author.

His [5] performed experiments similar to those of Freudweiler on rabbits. The results were nearly the same. His concluded that uric acid and urates act partly as foreign bodies and partly as toxic agents.

According to Spiegelberg,[6] subcutaneous injection of urates

[1] W. Ebstein. Ueber den gichtischen Prozess. Verhandl. des 2t Kongr. für innere Medizin, 79 (1882), and

Ibid. The Regimen to be Adopted in Cases of Gout. Transl. by J. Scott. London, 1885, and

Ibid. La Goutte, sa nature et son traitement. Transl. by E. Chambard. Paris, 1887, also

Ibid. Beiträge zur Lehre von der harnäsuren Diathese. Wiesbaden (1891).

[2] W. Ebstein und A. Nicolaier. Ueber die Ausscheidung der Harnsäure durch die Nieren. Virchow's Archiv, 143, 337 (1896).

[3] R. Heidenhain und A. Neisser. Versuche über den Vorgang der Harnabsonderung. Pflüger's Archiv, 9, 1 (1874).

[4] M. Freudweiler. Experimentelle Untersuchungen über das Wesen der Gichtknoten. Deutsche Arch. für klin. Medizin, 63, 266 (1899), also

Ibid. Experimentelle Untersuchungen über die Entstehung der Gichtknoten. Deutsche Arch. für klin. Medizin, 68, 155 (1900).

[5] W. His. Das Verhalten der Harnsäure im thierischen Organismus. Verhandl. des 17t Kongr. für innere Medizin (1899), 315, and

Ibid. Schicksal und Wirkungen des säuren härnsauren Natrons in Bauch- und Gelenkhöhle des Kaninchens. Deutsche Arch. für klin. Medizin, 67, 81 (1900).

[6] H. Spiegelberg. Ueber den Harnsäureeinfarkt der Neugeborenen. Arch. für exp. Path. u. Pharm., 41, 428 (1898).

causes formation of concretions only in young rabbits, not in full-grown ones.

Croftan [1] could not find any uric acid in the internal organs after injecting it into rabbits. According to Hager,[2] Carbone and Generali did not succeed in obtaining a precipitation of urates by the injection of uric acid and urates. Hager does not state what kind of animal was used in the experiments. Ebstein and Nicolaier [3] fed 10 grams uric acid per day to a dog for a period of five months and a half without obtaining a urate deposit. Croftan [4] likewise could not find any toxic effect or any changes in the organs of dogs after feeding them uric acid, as well as injecting it into them for long periods.

Pfeiffer [5] studied the subjective symptoms caused by uric acid and urates in man. According to this author, after the injection of a sterile solution of sodium chloride containing uric acid in suspension, pain does not begin until from twelve to twenty-four hours. It lasts for a few days. If doses of HCl or phosphoric acid be given at the time of the injection and for a little time before and after, either there is no pain, or it does not begin for a much longer period. If alkalies instead of acids be administered, then, according to Pfeiffer, the pain begins very soon after the injection. A solution of the urate causes pain almost immediately when injected.

Pfeiffer believes that his experiments indicate that the soluble urate only, and not the insoluble uric acid, is toxic. The uric acid becomes toxic only when it goes into solution in the body. The administration of acids by increasing the acidity of the fluids of the body prevents the solution of the uric acid. The administration of alkalies, on the other hand, hastens the solution of the uric acid.

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[1] A. Croftan. Synopsis of Experiments on the Transformation of Circulating Uric Acid in the Organism of Man and Animals. Med. Record, 64, 6 (1903).

[2] Carbone and Generali. July Meeting of the Turin Medical Academy, according to O. Hager. Zur Pathogenese der Gicht. München med. Wochenschrift, 47, 1101 (1900).

[3] W. Ebstein und A. Nicolaier. Ueber die Ausscheidung der Harnsäure durch die Nieren. Virchow's Archiv. 143, 337 (1896).

[4] A. Croftan. An Investigation into the Cause of So-called Uric Acid Lesions and a Rational Therapeutics of the Uratic Diathesis. N. Y. Med. Journ., 72, 221 (1900).

[5] E. Pfeiffer. Die Natur und Behandlung der Gicht. Verhandl. des 8t Kongr. für innere Medizin (1889), 166, also

Ibid. Die Gicht und ihre erfolgreich Behandlung. Wiesbaden (1891), 2d ed., also

Ibid. Ueber Harnsäure und Gicht. Berl. klin. Wochenschrift, Vol. 29, pp. 383, 412, 461, 490, and 536 (1892), also

Ibid. Ueber die Ausscheidung im Urin während des acuten Gichtanfalles mit beson. derer Berücksichtigung der Harnsäure. Berl. klin. Wochenschrift, 33, 319 (1896).

We know, of course, that we cannot influence directly the reaction of the fluids of the body in the manner indicated by Pfeiffer. Furthermore, His [1] and Freudweiler [2] have shown that the solution of the urate deposits is brought about by the vital action of the phagocytes. Freudweiler [2] showed that acids and alkalies do not affect the rate of absorption, and Freudberg [3] that we cannot influence the reaction of the blood by administration of alkalies or acids.

In Pfeiffer's experiments, his judgment may have been biased by the fact that he was trying to prove his theory. If his observations were correct, his explanations, at any rate, are wrong.

Mordhorst's [4] experiments indicate that sodium acid urate is not toxic. Uric acid dissolved in Na_2HPO_4 does not affect the eye of the rabbit any more than Na_2HPO_4 alone, or any more even than common drinking water.

According to Ebstein,[5] concretions of urates are found in gout only in dead, necrosed tissue. Occasionally the necrosed area extends beyond the urate crystals, but the urates are never found in healthy tissue. Bowlby,[6] too, found urates deposited only in dead, necrosed tissue. Von Noorden [7] and Schreiber [8] state that necrosis precedes deposition of urates in gout, but this seems to be merely an expression of opinion. They do not offer any experimental proof of their own.

Pfeiffer [9] states that uric acid and sodium acid urate do not cause necrosis when introduced into the body. He believes that in gout the necrosis precedes the deposition of the urates.

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[1] W. His. Das Verhalten der Harnsäure im thierischen Organismus. Verhandl. des 17t Kongr. für innere Medizin, 315 (1899), also

Ibid. Schicksal und Wirkungen des säuren harnsäuren Natrons im Bauch- und Gelenkhöhle des Kaninchens. Deutsche Arch. für klin. Medizin, 67, 81 (1900).

[2] M. Freudweiler. Experimentelle Untersuchungen über die Entstehung der Gichtknoten. Deutsche Arch. für klin. Medizin, 68, 155 (1900), also

Ibid. Deutsche Arch. für klin. Medizin, 63, 266 (1899).

[3] Freudberg. Ueber den Einfluss von Säuren und Alkalien auf die Alkalescenz des Blutes und die Reaktion des Harnes. Virchow's Archiv, 125, 566 (1891).

[4] Mordhorst. Zur Entstehung der Uratablagerung bei Gicht. Virchow's Archiv, 148, 285 (1897).

[5] W. Ebstein. Beiträge zur Lehre von der harnsäuren Diathese. Wiesbaden (1891), also

Ibid. Ueber den gichtischen Process. Verhandl. des 2t Kongr. für innere Medizin (1882), 79.

[6] A. Bowlby. Surgical Pathology and Morbid Anatomy, p. 311, London (1887).

[7] C. von Noorden. Lehrbuch der Pathologie des Stoffwechsels. Berlin (1893).

[8] E. Schreiber. Ueber die Harnsäure unter physiologischen und pathologischen Bedingungen, p. 102. Stuttgart (1899).

[9] E. Pfeiffer. Die Gicht und ihre erfolgreich Behandlung. Wiesbaden (1891), 2d ed.

According to the experiments of Freudweiler [1] and His,[2] on the other hand, uric acid and urates are slightly toxic and cause a necrosis. His confirmed the observation of Ebstein that necrosis is sometimes found in the tissue surrounding the concretions, but considered this a confirmation of his own view. According to His, the effect on the surrounding tissue is due to the urate in solution, but the necrosis is secondary to the formation of the deposit. A small quantity of the deposit at the periphery of the concretions goes into solution, and the solution exerts a slight toxic action on the surrounding tissue.

It seems to be fairly well settled that necrosis does not necessarily precede deposition of urates in gout. Thus Ranvier [3] and Rindfleisch [4] found gouty cartilage cells normal in spite of the presence of urates. Duckworth [5] and Luff [6] found gouty concretions in healthy tissue. Riehl,[7] too, found urates in healthy tissue in gout. He attributes Ebstein's error in this respect to the same cause as in his experiments on birds. When the section is brought into contact with water, the urates at the periphery of the crystal mass dissolve, leaving a space between the concretion and the tissue. This is the space that Ebstein looked upon as necrosed. Aschoff [8] found urates deposited in the kidney in healthy tissue. Bennecke [9] never found necrosis extending beyond the crystalline mass of urates. Minkowski [10] has repeated this work and found the urate concretions in healthy tissue.

According to Riehl,[7] Freudweiler,[1] and His,[2] the tissue change

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[1] M. Freudweiler. Experimentelle Untersuchungen über das Wesen der Gichtknoten. Deutsche Arch. für klin. Medizin, 63, 266, (1899), also

Ibid. Experimentelle Untersuchungen über die Entstehung der Gichtknoten. Deutsche Arch. für klin. Medizin, 68, 155 (1900).

[2] W. His. Das Verhalten der Harnsäure im thierischen Organismus. Verhandl. des 17t Kongr. für innere Medizin (1899), 315, also

Ibid. Schicksal und Wirkungen des säuren harnsäuren Natrons in Bauch- und Gelenkhöhle des Kaninchens. Deutsche Arch. für klin. Medizin, 67, 81 (1900).

[3] Ranvier. Manuel d'Histologie pathologique (1869).

[4] Rindfleisch. Lehrbuch der pathologischen Gewebelehre. Leipzig (1886).

[5] D. Duckworth. A Treatise on Gout. London (1890).

[6] A. Luff. The Chemistry and Pathology of Gout. (Croonian Lectures.) Lancet (1897), I, 857, 942, and 1069.

[7] G. Riehl. Zur Anatomie der Gicht. Wien. klin. Wochenschrift, 10, 761 (1897), also, Ueber die Anatomie der Gichtknoten. Vortrag gehalten in der Leipziger medizin, Gesellschaft, 9 Febr. (1897), Schmidt's Jahrb., 253, 271 (1897).

[8] L. Aschoff. Verhandl. der Deutsch. patholog. Gesellsch. München, I (1899), and II (1900).

[9] E. Bennecke. Beiträge zur Anatomie der Gicht. Arch. für klin. Chir., 66, 658 (1902).

[10] O. Minkowski. Die Gicht. In Nothnagel's specielle Pathologie und Therapie, VII Band, III Theil, p. 220 (1903).

which they speak of as a necrosis is secondary and caused by the urate, partly by its action as a foreign body, and partly by its toxic action.

Litten [1] did not believe that the tissue in gout is really necrosed. Minkowski,[2] too, states that the tissue surrounding gouty concrements is not really necrosed. It does not stain like necrosed tissue.

According to Beckart,[3] the anatomical lesions in gout are not such as would be produced by an acid, but look rather like the slow, degenerative changes that occur in other forms of disease. The author states that the lesions minus the urate deposits are described by Ziegler [4] as the constant substratum of arthritis deformans.

Mordhorst [5] says that hyaline degeneration is a good name for the lesion. Necrosed tissue decomposes, is absorbed, and replaced by cicatricial tissue. According to this author, in the case of gout, the tissue surrounding the urates changes to a hyaline mass. Similarly, in the guanin gout of hogs, there is no necrosis, according to Mendelsohn,[6] but an amyloid degeneration difficult to describe.

It can be seen that we have not yet a perfectly clear understanding of the interaction of tissue and urates. It seems to be certain that urates can deposit in healthy tissues, and that they cause some kind of change which is probably not a necrosis. But it may also be true that a slight tissue change of some sort precedes the deposition of the urates, and that when a crystal is deposited in a small lesion it grows by accretion and extends into healthy tissue. Experiments have not yet shown that this latter possibility can be excluded. Likhatscheff [7] has suggested

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[1] M. Litten. Pathologisch-anatomische Beobachtungen. Ein Fall von schwerer Gicht mit Amyloiddegeneration. Virchow's Archiv, 66, 129 (1876).

[2] O. Minkowski. Die Gicht. In Nothnagel's Specielle Pathologie und Therapie (1903), VII Band, III Theil, p. 223 (1903).

[3] J. Beckart. On the Pathology of the Gouty Paroxysm. Brit. Med. Journ., 1, 243 (1895).

[4] E. Ziegler. Ueber die subchondralen Veränderungen der Knochen bei Arthritis deformans und über Knochencysten. Virchow's Archiv, 70, 502 (1877).

[5] Mordhorst. Zur Entstehung der Uratablagerungen bei Gicht. Virchow's Archiv, 148, 285 (1897).

[6] W. Mendelsohn. On guanin gout in the hog, and its relation to the sodium urate gout of man. Am. Journ. of Med. Sciences, N. S., 95, 109 (1888).

[7] A. Likhatscheff. Experimentelle Untersuchungen über die Frage der Ureterenunterbindung bei Hühnern mit besonderer Berücksichtigung der nachfolgenden Uratablagerung. Ziegler's Beiträge zur patholog. Anatomie und allgem. Pathologie, 20, 102 (1896).

that the urates do not cause the tissue change nor the tissue change the deposition of the urates, but that both are due to a common cause.

Gout

Analysis of Concrements

Lehmann, Laugier, and Wurzer give the following analyses of gouty concretions: [1]

	Lehmann	Laugier	Wurzer
Sodium acid urate	52.12%	.....	.....
Uric acid	.....	16.7%	20.0%
Calcium acid urate	1.25	.....	.....
Soda	.....	16.7	20.0
Sodium chloride	9.84	16.7	18.0
Lime	.....	8.3	10.0
Calcium phosphate	4.32	.....	.....
Cellular tissue	28.49	.....	.....
Animal matter	.....	16.7	19.5
Potassium chloride	.....	.....	2.2
Water	.....	8.3	10.3
Loss	.....	16.6	.....
Water, loss, etc.	3.98	.....	.....

An analysis of L'heritier [1] shows:

Urates of ammonia, sodium, and lime	49.0%
Phosphate of lime	42.0
Organic matter and water	9.0

In a gouty concretion Marchand found: [2]

Sodium acid urate	34.20%
Calcium acid urate	2.12
Ammonium carbonate	7.86
Sodium chloride	14.12
Animal matter	32.53
Water	6.80
Loss	2.37

Two analyses of Ebstein and Sprague [3] show:

Uric acid	59.7%	61.27
Animal matter	27.88	26.45
Na_3O	9.3	12.28
K_2O	2.95	
CaO	.17	
Mg, Fe, P_2O_5, & S	trace	

[1] Becquerel and Rodier. Pathological Chemistry. London (1857), 515.

[2] R. Marchand. Lehrbuch der physiologischen Chemie. Berlin (1844), p. 107.

[3] W. Ebstein und C. Sprague. Beiträge zur Analyse gichtischer Tophi. Virchow's Archiv, 125, 207 (1891).

In these analyses the uric acid means uric acid combined with bases. The concretions are chiefly sodium acid urate and organic matter.

Uric Acid in the Blood

Although the presence of uric acid in gouty blood had previously been suspected, it was first found by Garrod in 1848.[1] This author was able to demonstrate by the so-called thread experiment that uric acid is always present in the blood during acute attacks of gout. If a thread which has been dipped in blood containing uric acid and acidified with acetic acid be allowed to dry, uric acid crystals will form on the thread, and can be seen under the microscope. According to Garrod, uric acid likewise is found in the blood in chronic gout,[1,2] but not in the intervals between attacks in acute gout. He did not find uric acid in the blood in health.

Jones,[3] Ranke,[4] Charcot,[5] Cantani,[6] and Salomon [7] confirmed the discovery of uric acid in the blood either by the thread experiment or by precipitation with acid. Abeles [8] and Strauss [9] found uric acid in gouty blood by the murexid test. Klemperer [10] found from .07 to .09 gram uric acid in 1,000 cc. of blood taken during an acute attack of gout. According to Magnus-Levy,[11] there is as much uric acid in gouty blood between attacks as during acute attacks.

Gairdner [12] and Meldon [13] have each reported a case where uric

[1] A. Garrod. Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism, and Bright's Disease. Medico-Chirurgical Trans., 31, 83 (1848).

[2] *Ibid.* The Nature and Treatment of Gout and Rheumatic Gout. London (1859).

[3] H. Jones. A Treatise of Gravel, Calculus, and Gout.

[4] Ranke. Beobachtungen und Versuche über die Ausscheidung der Harnsäure beim Menschen. München (1858).

[5] Charcot. Du rheumatisme nouex et de la goutte. Gazette des hôpiteaux, 1866 and 1867.

[6] A. Cantani. Oxalurie, Gicht, und Steinkrankheiten. Specielle Pathologie und Therapie der Stoffwechselkrankheiten. German translation by H. Hahn (1880).

[7] G. Salomon. Ueber pathologisch-chemische Blutuntersuchungen. Charité Annalen, 5, 137 (1880).

[8] M. Abeles. Ueber Harnsäure im Blute und einigen Organen und Geweben. Wien. med. Jahrb., 83, 497 (1887).

[9] H. Strauss. Die chronischen Nierenentzündungen und ihre Einwirkungen auf die Blutflussigkeit. Berlin (1902).

[10] G. Klemperer. Zur Pathologie und Therapie der Gicht. Vortrag. geh. in der Verein für innere Med. zu Berlin, 1895. Deutsche med. Wochenschrift, 21, 655 (1895).

[11] A. Magnus-Levy. Harnsäuregehalt und Alkalescenz des Blutes in der Gicht. Verhandl. des 16t Kongr. für innere Medizin (1898), 266, also

Ibid. Ueber Gicht. Zeitschr. für klin. Med., 36, 412 (1898).

[12] W. Gairdner. On Gout, its History, its Causes, and its Cure. 4th ed. London (1860).

[13] A. Meldon. Pathology and Treatment of Gout. Brit. Med. Journ. (1881), I, 466.

acid was found in healthy blood. They did not state their method of analysis. Weintraud [1] found uric acid in the blood of a healthy man after a meal of thymus. Croftan [2] states that he found .02 to .03 gram uric acid in a hundred grams of blood. This is more than any author has reported, even in gouty blood, and is more than Roberts [3] found can be dissolved in the blood. Croftan analyzed the serum plus the blood corpuscles, however, and as he does not state his method of analysis, it seems possible that the purin bases in the corpuscles may have come into the analysis.

Neither von Jaksch,[4] Bain,[5] nor Klemperer [6] could find uric acid in any of the healthy blood which they examined.

Uric acid has been found in the blood in diseases other than gout. Garrod [7] found uric acid in the blood by the thread experiment in acute rheumatism, albuminuria, and chronic lead poisoning. Salomon [8] found it in the blood in pneumonia, anemia, and phthisis. According to Haig,[9] uric acid is found in the blood in pneumonia and certain other diseases. Haig used the Haycraft method of analysis, however, and this method gives the purin bases as well as uric acid. Von Jaksch [10] found uric acid in the blood in nephritis, lead poisoning, malaria, typhus, liver carcinoma, intestinal inflammation, anemia, and pneumonia, and in conditions of emphysema and dyspnea occasionally. Magnus-Levy's experiments show the presence of uric acid in

[1] W. Weintraud. Ueber Harnsäure im Blute und ihre Bedeutung für die Entstehung der Gicht. Wien. klin. Rundschau, 10, p. 3 and 21 (1896).

[2] A. Croftan. An Investigation into the Causes of So-called Uric Acid Lesions and a Rational Therapeutics of the Uratic Diathesis N. Y. Med. Journ., 72, 221 (1900).

[3] W. Roberts. On the Chemistry and Therapeutics of Uric Acid, Gravel, and Gout. (Croonian Lectures for 1892.) Lancet, I, 1345 and 1399, and II, 69, 127 (1892).

[4] von Jaksch. Ueber die klinische Bedeutung des Vorkommens von Harnsäure und Xanthinbasen im Blute, den Exudaten und Transudaten. Zeitschr. für Heilk., 11, 415 (1890).

[5] W. Bain. An Experimental Contribution to the Study of Gout. Brit. Med. Journ. (1899), II, 1164.

[6] G. Klemperer. Zur Pathologie und Therapie der Gicht. Deutsche med. Wochenschrift, 21, 655 (1895).

[7] A. Garrod. Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism, and Bright's Disease. Medico-Legal Transactions, 31, 83 (1848), also

Ibid. The Nature and Treatment of Gout and Rheumatic Gout. London (1848).

[8] G. Salomon. Ueber die Verbreitung und Entstehung von Hypoxanthin und Milchsäure im thierischen Organismus. Zeitschr. für physiol. Chem., 2, 65 (1878).

[9] A. Haig. Uric Acid as a Factor in the Cause of Disease. 3d ed. Phila. (1896).

[10] R. von Jaksch. Ueber Uricacidaemie. Deutsche med. Wochenschrift, 16, 741 (1890), also Ueber die klinische Bedeutung des Vorkommens von Harnsäure und Xanthinbasen im Blute, den Exudaten und Transudaten. Zeitschr. für Heilk., 11, 415 (1890).

the blood in various kidney diseases, lead colic, pneumonia, phthisis, arteriosclerosis, bronchitis, and emphysema [1] and in leukemia.[2] Klemperer [3] has found about .1 gram uric acid in 1,000 cc. of leukemic blood, and even a larger quantity in the blood in a patient with nephritis. This is more than he found in the blood of his gouty patients. Petrén [4] found uric acid in the blood in pneumonia, hysterical vomiting, and gonorrheal rheumatism. In cases of Bright's disease, malignant disease, aneurism of the aorta, ulcerative endocarditis, and pneumonia, Watson [5] found uric acid in the blood after death.

Wolf [6] and Tichborne [7] state that they found uric acid in the perspiration of gouty patients. Lecorché,[8] Lehmann,[9] Garrod,[10] and Magnus-Levy [1] could not confirm this discovery.

We can say, then, that uric acid is found in the blood in gout and in a few other diseases, but probably not generally in health.

Alkalinity of the Blood in Gout

An assumption upon which many authors have based their theories of gout is that the alkalinity of the blood is decreased in this disease. This assumption has never been found true experimentally, even by inaccurate methods of analysis. The alkalinity of the blood in gout has never been determined by an accurate method, that is, by a method which gives the "actual" concentration of the hydroxyl ions. It is extremely doubtful that a decrease in the real alkalinity would be found. The normal alkalinity of the blood is so extremely small that it would need but a slight decrease in the concentration of the hydroxyl ions to make the blood neutral or even acid.

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[1] A. Magnus-Levy. Ueber Gicht. Zeitschr. für klin. Med., 36, 412 (1898).

[2] *Ibid.* Ueber den Stoffwechsel bei acuter und chronischer Leukämie. Virchow's Archiv, 152, 107 (1895).

[3] G. Klemperer. Zur Pathologie und Therapie der Gicht. Deutsche med. Wochenschrift, 21, 655 (1895).

[4] K. Petrén. Ueber das Vorkommen von Harnsäure im Blute bei Menschen und Säugethieren. Arch. für exp. Path. u. Pharm., 41, 265 (1898).

[5] C. Watson. Observations on General Metabolism and the Blood in Gout. Brit. Med. Journ., 110 (1900).

[6] Wolf. Diss. sist. casum. Calculositats. Tübingen, 1817.

[7] C. Tichborne. On the Elimination of Uric Acid by the Skin, and the Difficulty of Detecting Minute Quantities of that Acid. Brit. Med. Journ. (1887), II, 1097.

[8] Lecorché. Traité de la Goutte. Paris (1884).

[9] Lehmann. Physiol. Chem. (1855).

[10] A. Garrod. On the Blood and Effused Fluids in Gout, Rheumatism, and Bright's Disease. Medico-Legal Transactions, 37, 49 (1854).

Drouin,[1] Luff,[2] Strauss,[3] Watson,[4] and Magnus-Levy,[5] who used titration methods, did not find the blood alkalinity decreased, nor did Klemperer,[6] who took the content of CO_2 as a measure of the blood alkalinity. A tendency toward decreased alkalinity of the blood is sometimes accompanied by increased ammonia in the urine. Neither Magnus-Levy [5] nor Vogel [7] could find increased ammonia in the urine in gout. Soetbeer [8] found less ammonia in the urine of gouty patients living on the same diet than in that of normal patients.

Only Pfeiffer [9] and Aronsohn [10] have assumed that the alkalinity of the blood is increased in gout. We have seen that they have offered no direct evidence in favor of this view, and the only indirect evidence they have offered is exceedingly bad.

Solubility of Uric Acid in the Blood and Tissues

We have already stated that Roberts [11] found that the presence of sodium salts decreases the solubility of sodium acid urate solution. He found that a solution of one part sodium acid urate in 6,000 of blood serum is saturated. Klemperer [12] found .17 gram uric acid soluble in 100 cc. of blood serum. It seems probable

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[1] R. Drouin. Hemoalkalimétrie. Paris, 1892.

[2] A. Luff. The Alkalinity of the Blood in Gout. Brit. Med. Journ., 1, 1066 (1898), and *Ibid.* Gout: Its Pathology and Treatment. New York (1899).

[3] H. Strauss. Ueber das Verhalten der Blutalkalescenz des Menschen unter einigen physiologischen und pathologischen Bedingungen. Zeitschr. für klin. Med., 30, 317 (1896).

[4] C. Watson. Observations on General Metabolism and the Blood in Gout. Brit. Med. Journ., 1, 10 (1900).

[5] A. Magnus-Levy. Ueber Gicht. Zeitschr. für klin. Med., 36, 412 (1898).

[6] G. Klemperer. Zur Pathologie und Therapie der Gicht. Deutsche med. Wochenschrift, 21, 665 (1895).

[7] L. Vogel. Ueber den Stoffwechsel bei Gichtkranken. Enthalten in einem Vortrag von Noorden's Beiträge zur Ernährungenslehre nach Versuchen von Dr. Kayser, Krug, Dapper, u. Vogel. Sitzungsber. der physiol. Gesellsch., Berl., 17 Febr., 1893, and Du Bois Archiv, 377 (1893), also

Ibid. Ueber Gicht, in von Noorden's Beiträge zur Lehre vom Stoffwechsel. Berl. (1894), H. 2, p. 113.

[8] F. Soetbeer. Ein Stoffwechselversuch bei Gicht. Zeitschr. für physiol. Chem., 40, 55 (1903).

[9] E. Pfeiffer. Die Gicht und ihre erfolgreich Behandlung. Wiesbaden (1891), 2d ed.

[10] E. Aronsohn. Zur Natur und Behandlung der Gicht und über die Bedeutung der Emser Wilhelmsquelle. Deutsche med. Wochenschrift, 16, 381 (1890).

[11] W. Roberts. On the Chemistry and Therapeutics of Uric Acid, Gravel, and Gout. (Croonian Lectures for 1892.) Lancet (1892), I, 1345 and 1399, and II, 69 and 127.

[12] G. Klemperer. Zur Pathologie und Therapie der Gicht. Deutsche med. Wochenschrift, 21, 655 (1895), and

Ibid. Untersuchungen über Gicht und harnsäuren Nierensteine. Berlin (1896).

that Klemperer's figures for the solubility of uric acid in blood serum are rather high, unless we assume that the uric acid combines organically with some compound in the blood. Sodium acid urate is soluble only in 1,100 to 1,200 parts of water at the room temperature. Klemperer's results would indicate that this salt is soluble in about 600 parts of blood serum, whereas we should expect it to be rather less soluble in blood serum than in water.

According to Klemperer, gouty blood is not nearly saturated with uric acid. The amount of uric acid in gouty blood is so small in comparison with its solubility that such blood can dissolve practically the same quantity of uric acid as normal blood free from uric acid.

Luff [1] has shown that sodium acid urate is not less soluble in blood serum which has been one fourth, one half, or even three fourths neutralized with hydrochloric acid or tartaric acid. In fact, the urate seems to be even slightly more soluble in the less alkaline serum. This author found that meat ash decreases the solubility of the urate in blood serum, but that vegetable ash does not. He studied the chemistry of these ashes and made experiments with pure salts and mixtures of salts, but could not determine the reason for the difference in action of the ashes.

It is plain that those theories which assume that the alkalinity of the blood is decreased in gout, or that the blood is saturated with uric acid, and that on this account uric acid precipitates out, are based on erroneous notions.

It will be remembered that Goto and Minkowski had expressed the view that uric acid might exist in the body in combination with thymic acid or nucleic acid. Schmoll [2] has suggested the possibility that uric acid normally circulates in the blood in combination with thymic acid, and that in gout it is free and not combined with thymic acid. He supposes that in health uric acid is formed only by oxidation from the nucleoproteids, and that thymic acid is always formed at the same time to combine with it, but that in gout uric acid is formed by synthesis and that no thymic acid is formed at the same time. The evidence he offers in support of his theory is the slight increase in the excretion of uric

[1] A. Luff. The Chemistry and Pathology of Gout. (Goulstonian Lectures.) Lancet (1897), I, 857, 942, and 1069, and Gout, Its Pathology and Treatment. New York (1899).

[2] F. Schmoll. Sur la formation de l'acide urique dans la goutte et les causes de sa precipitation dans les tissus. Arch. gén. de med., 2, 2433 (1904).

acid that he sometimes found after use of thymic acid, and the fact that, according to him, the uric acid excretion can be increased by adding casein to the food, a fact which led him to believe that uric acid can be formed by synthesis in the body.

In regard to the synthesis of uric acid, it will be remembered that we have a mass of evidence to oppose Schmoll's view. The increased excretion of uric acid after thymic acid feeding was only slight and not present in all cases. In regard to thymic acid, we know that the general opinion is that nucleic acid cannot be further decomposed into a definite body (thymic acid) free from purin bases. We have also the experiments of Schittenhelm and Bendix,[1] which would seem to indicate that nucleic acid does not act as a solvent for uric acid in the organism.

Metabolism in Gout

METABOLISM OF URIC ACID

Garrod,[2] who used the inaccurate Heinz method of analysis, found the excretion of uric acid diminished in gout. This is one of the points on which he based his theory of this disease. Other experimenters who used the Heinz method, among whom were Böcker,[3] Lehmann,[4] Ranke,[5] Braun,[6] Bartels,[7] Cantani,[8] and Lecorché[9] confirmed Garrod. Bouchard[10] found the excretion of uric acid low[10] except in the first few days[11] of an acute attack. Fawcett[12] found the excretion of uric acid just a little low in gout.

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[1] A. Schittenhelm und E. Bendix. Ueber das Schicksal der in die Blutbahn eingebrachten Nukleinsäure, 30, 1164 (1904).

[2] A. Garrod. Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism, and Bright's Disease. Medico-Chirurg. Trans., 31, 83 (1848), also *Ibid.* The Nature and Treatment of Gout and Rheumatic Gout. London, 1859.

[3] Böcker. Zur Pathologie der Gicht. Rhein. Monatsh., Feb. (1850), and Canstatt's Jahresber. (1850), 158.

[4] Lehmann. Lehrbuch der physiol. Chem., Vol. II (1853).

[5] Ranke. Beobachtungen und Versuche über die Ausscheidung der Harnsäure beim Menschen. München (1858).

[6] Braun. Beitrage zu einer Monographie der Gicht. Wiesbaden (1860).

[7] Bartels. Untersuchungen über die Ursachen einer gesteigerten Ausscheidung der Harnsäure in Krankheiten. Deutsche Arch. für klin. Medizin, I, 13 (1866).

[8] Cantani. Specielle Pathologie und Therapie der Stoffwechselkrankheiten. German translation by Hahn (1880), Bd. II.

[9] Lecorché. Traité theorique et practique de la goute. Paris (1884).

[10] C. Bouchard. Leçons sur les maladies par ralentissement de la nutrition. 3 ed. Paris (1890).

[11] *Ibid.* Maladies par ralentissement de la nutrition. Paris (1882).

[12] J. Fawcett. On the Urinary Excretion in Gout and the Effect of Treatment with Colchicum and Salicylate of Soda. Guy's Hospital Reports, 52, 115 (1895).

The authors who have used an accurate method for determining uric acid, Levison,[1] Schmoll,[2] Camerer,[3] Badt,[4] Klemperer,[5] Martin,[6] Zagari,[7], and Bain,[8] could not find that the excretion of uric acid is decreased in gout. Kaufmann and Mohr[9] and Grossman[10] have found the exogenous uric acid in gout about the same as in normal patients.

Pfeiffer[11] was the first to call attention to the fact that the excretion of uric acid is higher in an acute attack of gout than in the interval between attacks. The author, unfortunately, used the inaccurate Heinz method of analysis, but his discovery has been confirmed by Magnus-Levy,[12] who determined the uric acid by an accurate method. Vogel[13] found that there is a gradual increase in the daily excretion of uric acid for several days after

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[1] F. Levison. The Uric Acid Diathesis, Gout, Sand, and Gravel. Transl. by L. Scott. London (1894).

[2] E. Schmoll. Stoffwechselversuch an einem Gichtkranken. Zeitschr. für klin. Med., 29, 510 (1896).

[3] Camerer. Beitrag zur Erforschung der Stickstoffhaltigen Bestandtheile des menschlichen Urins, insbesondere der sogenannten Alloxurkörper. Zeitschr. für Biol., 35, 206 (1897), also

Ibid. Der Gehalt des menschlichen Urins an stickstoffhaltigen Körpern, seine Acidität: die Acidose bei der Urinanalyse. Tübingen (1901).

[4] L. Badt. Harnsäure oder Alloxurdiathese? Zeitschr. für klin. Med., 34, 359 (1898), also

Ibid. Ueber Harnsäureausscheidung im Urin während des acuten Gichtanfalles Zeitschr. für klin. Med., 57, 546 (1899).

[5] Klemperer. Zur Pathologie und Therapie der Gicht. Deutsche med. Wochenschrift, 21, 655 (1895).

[6] C. Martin. Ueber die Ausscheidungsverhältnisse der Alloxurkörper bei Nephritis Centralblatt für innere Medizin, 20, 625 (1899).

[7] G. Zagari. Il Bilancio organico di un Gottosa durante e fuori l'accesso. Napoli (1898).

[8] W. Bain. The Action of Various Drugs and Diets on the Excretion of Nitrogen in Gout. Brit. Med. Journ. (1900), I, 834.

[9] M. Kaufmann und L. Mohr. Beiträge zur Alloxurkörperfrage und zur Pathologie der Gicht. II Theil. Ueber Alloxurkörperausscheidung unter pathologischen Verhaltnissen. Deutsche Arch. für klin. Medizin, 74, 348 (1902).

[10] W. J. Grossman. Zur Kenntniss des Harnsäurestoffwechsels und des Harnindicans bei Gichtkranken. Berl. klin. Wochenschrift, 40, 539 (1903).

[11] E. Pfeiffer. Die Natur und Behandlung der Gicht. Verhandl. des 8t Kongr. für innere Medizin (1889), p. 166, also

Ibid. Die Gicht und ihre erfolgreich Behandlung. Wiesbaden (1891), 2 Aufl., and

Ibid. Ueber die Ausscheidung im Urin während des acuten Gichtanfalles mit besonderer Beruchtsichtigung der Harnsäure. Berl. klin. Wochenschrift, 33, 319 (1896).

[12] A. Magnus-Levy. Ueber Gicht. Zeitschr. für klin. Med., 36, 412 (1898), and Beitrage zum Stoffwechsel bei Gicht. Berl. klin. Wochenschrift, 33, pp. 389 and 416 (1896).

[13] L. Vogel. Ueber Gicht. Zeitschr. für klin. Med., 24, 512 (1894), also

Ibid. Ueber den Stoffwechsel bei Gichtkranken. Enthalten in einem Vortrag v. Noorden's Beiträge zur Ernährungslehre nach Versuchen von Dr. Kayser, Krug, Dapper, Vogel. Sitzungsber. der physiol. Gesellsch., Berl., 17 Febr., 1893; Du Bois Archiv, 377 (1893), and in von Noorden's Beitrage zur Lehre vom Stoffwechsel., Berl. (1894), H. 2.

the onset of an acute attack. Watson [1] confirmed both Magnus-Levy and Vogel. His [2] found that the daily excretion of uric acid is decreased for two or three days before the acute attack. With the onset of the attack, excretion of uric acid begins to increase. The increase reaches a maximum in from one to five days, and then gradually decreases to the normal value. This work of His has been confirmed in detail by Waldvogel [3] and by Futcher.[4]

After feeding thymus or nuclein, there is an increased excretion of uric acid in gout as in health, according to the experiments of Klemperer,[5] ten Cate,[6] Bain,[7] Watson,[8] and Schmoll.[9] Vogt [10] and Reach [11] observed an increased excretion of uric acid after nuclein in gout, but the quantity of uric acid as excreted was not so great as after the same quantity of nuclein in health.

Soetbeer [12] carried out a series of experiments on gouty patients, and compared his results with those obtained by Pfeil [13] on healthy subjects. He collected the urine for analysis at intervals of three

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[1] C. Watson. Observations on General Metabolism and the Blood in Gout. Brit. Med. Journ., 1, 10 (1900).

[2] W. His. Untersuchungen an Gichtkranken. Wien. med. Blatter, 19, 291 (1896), also

Ibid. Untersuchungen an Gichtkranken. Deutsche med. Wochenschrift, 22, 186 Ver. (1896), also

Ibid. Die Ausscheidung von Harnsäure im Urin der Gichtkranken mit besonderer Berücksichtigung der Anfallzeiten und bestimmter Behandlungsmethoden. Deutsche Arch. für klin. Medizin, 65, 156 (1900).

[3] Waldvogel. Der Stoffwechsel im Gichtanfall. Centralbl. für Stoffwechsel und Verdauungskrankheiten, 3, 1 (1902).

[4] F. Futcher. Some Points on the Metabolism in Gout; with Special Reference to Relationship between the Uric Acid and the Phosphoric Acid Elimination in the Intervals and during Acute Attacks. Practitioner, London, 71, 181 (1903).

[5] G. Klemperer. Zur Pathologie und Therapie der Gicht. Deutsche med. Wochenschrift, 21, 665 (1895).

[6] B. ten Cate. Beiträge zur gichtischen Diathese. Inaug. Dissert., Göttingen (1899).

[7] W. Bain. An Experimental Contribution to the Study of Gout. Brit. Med. Journ. (1899), II, 1164.

[8] C. Watson. Metabolism in Gout with Observations on the Action of Salicylate of Soda and Nucleic Acid. Journ. of Path., 7, 103 (1901).

[9] E. Schmoll. Stoffwechselversuch an einem Gichtkranken. Zeitschr. für klin. Med., 29, 510 (1896), also

Ibid. Einige Bemerkungen zur Therapie der Gicht. Centralblatt für innere Medizin, 19, 1065 (1898).

[10] H. Vogt. Ein Stoffwechselversuch bei acute Gicht. Deutsche Arch. für klin. Medizin, 71, 24 (1901).

[11] F. Reach. Ein Beitrag zur Kenntniss des Stoffwechsels bei der Gicht. München med. Wochenschrift (1902), 1215.

[12] F. Soetbeer. Ueber die Einfluss der Nahrungsaufnahme auf die Ausscheidung der Harnsäure bei Arthritis urica. Zeitschr. für physiol. Chem., 40, 25 (1903).

[13] P. Pfeil. Ueber den Einfluss der Nahrungsaufnahme auf die Ausscheidung der Harnsäure. Zeitschr. für physiol. Chem., 40, 1 (1903).

hours. The results showed that the excretion of uric acid after food containing nucleins and purin bodies is not at all so high as in health, and that the increased excretion does not appear so soon. In some cases there was absolutely no increased excretion of uric acid after a change from a purin free diet to one containing purin bodies. The excretion of uric acid was found to be much lower in two gouty patients than in two healthy patients on the same diet.[1]

It will be well to speak here of Neusser's discovery.[2] This author observed granules around the nuclei of the leucocytes in gouty blood which stain black with Ehrlich's triacid mixture. This was interpreted to mean an overproduction of nuclein material. Futcher,[3] however, observed these granules in the leucocytes in other diseases, and did not always find them in gout. Ehrlich [4] thinks that the results of Neusser are due to the use of impure reagents.

METABOLISM OF PURIN BASES

Kolisch [5] found the uric acid excretion low and the excretion of purin bases high in gout, and attempted to base a theory of gout on his observations. Croftan [6] likewise found the ratio of the purin bases to uric acid high in gouty urine. Both of these experimenters used the inaccurate Krüger-Wulf method in their experiments, a fact which makes their work valueless. We have already seen that the uric acid excretion is not low in gout. Further, neither Zülzer,[7] Malfatti,[8] Laquer,[9]

[1] F. Soetbeer. Ein Stoffwechselversuch bei Gicht. Zeitschr. für physiol. Chem., 40, 55 (1903).

[2] E. Neusser. Ueber einen besonderen Blutbefund bei uratischer Diathese. Wien. klin. Wochenschrift, 7, 727 (1894).

[3] T. Futcher. Ueber den Zusammenhang zwischen der sogennanten perinuclear basophilie und der Ausschiedung der Alloxurkörper im Harn. Centralblatt für klin. Medizin, 17, 985 (1896).

[4] Ehrlich und Lazarus. Die Anämie. Nothnagel's Handbuch, Bd. 8, Wien (1898).

[5] R. Kolisch. Ueber Wesen und Behandlung der Gicht. Wien. klin. Wochenschrift, 8, 787 (1895), also,

R. Kolisch und Dostal. Das Verhalten der Alloxurkörper im pathologischen Harn. Wien. klin. Wochenschrift, 8, 413, and 435 (1895), also

R. Kolisch. Ueber Wesen und Behandlung der uratischen Diathese. Stuttgart (1895).

[6] A. Croftan. An Investigation into the Causes of So-Called Uric Acid Lesions and a Rational Therapeutics of the Uratic Diathesis. N. Y. Med. Journ., 72, 221 (1900).

[7] G. Zulzer. Ueber die Alloxurkörperausscheidung im Harn bei Nephritis. Berl. klin. Wochenschrift, 33, 72 (1896).

[8] H. Malfatti. Ueber die Alloxurkörper und ihr Verhältniss zur Gicht. Wien. klin. Wochenschrift, 9, 723 (1896).

[9] B. Laquer. Ueber die Ausscheidungsverhältnisse der Alloxurkörper im Harne von Gesunden und Kranken. Verhandl. des 14t Kongr. für innere Medizin, 333 (1896).

Schmoll,[1] Albu,[2] Camerer,[3] Strauss,[4] Badt,[5] Martin,[6] Bain[7] nor Kaufmann and Mohr[8] could find that the excretion of purin bases is increased, or that the ratio of the quantity of purin bases to uric acid is increased in gout.

METABOLISM OF NITROGEN AND FAT

Vogel[9] was the first to observe that there is a disturbance in the metabolism of nitrogen in gout. In one case he found a retention of 13.10 grams nitrogen during five days of an acute attack. In another case there was a retention of from one to seven grams a day for fourteen days. In a third case there was an average retention of from four to seven grams per day for ten days. Laquer,[10] Vogt,[11] and Schmoll[1] confirmed Vogel's observations. Schmoll[1] found a retention of 34 grams nitrogen in ten days.

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[1] E. Schmoll. Stoffwechselversuch an einem Gichtkranken. Zeitschr. für klin. Med., 29, 510 (1896), also

Ibid. Einige Bemerkungen zur Theorie der Gicht. Centralblatt für innere Medizin, 19, 1065 (1898).

[2] Albu, in Discussion of Laquer's article. Ueber die Ausscheidungsverhältnisse der Alloxurkörper im Harne von Gesunden und Kranken. Verhandl. des 14t Kongr. für innere Medizin, 423 (1896).

[3] Camerer. Beitrag zur Erforschung der stickstoffhaltigen Bestandtheile des menschlichen Urins, insbesondere der sogenannten Alloxurkörper. Zeitschr. für Biol., 35, 206 (1896).

[4] J. Strauss. Ueber die Einwirkung des kohlensäuren Kalkes auf den menschlichen Stoffwechsel, ein Beitrag zur Therapie der harnsäuren Nierenconcretionen nebst Bemerk ungen über Alloxurkörperausscheidung. Zeitschr. für klin. Med., 31, 493 (1897).

[5] L. Badt. Harnsäure oder Alloxurdiathese? Zeitschr. für klin. Med., 34, 359 (1898).

[6] C. Martin. Ueber die Ausscheidungsverhältnisse der Alloxurkörper bei Nephritis. Centralblatt für innere Medizin, 20, 625 (1899).

[7] W. Bain. An Experimental Contribution to the Study of Gout. Brit. Med. Journ. (1899), II, 1164, also

The Action of Various Drugs and Diets on the Excretion of Nitrogen in Gout. Brit. Med. Journ. (1900), 1, 834.

[8] M. Kaufmann und L. Mohr. Beiträge zur Alloxurkörperfrage und zur Pathologie der Gicht. II Theil. Ueber Alloxurkörperausscheidung unter pathologischen Verhältnissen. Deutsche Arch. für klin. Medizin, 74, 384 (1902).

[9] L. Vogel. Ueber den Stoffwechsel bei Gichtkranken. Enthalten in einem Vortrag v. Noorden's Beiträge zur Ernahrungslehre nach Versuchen von Dr. Kayser, Krug, Dapper, und Vogel. Sitzungsber. des physiol. Gesellsch., Berlin, 17 Febr., 1893; Du Bois Archiv, 377 (1893), also

In von Noorden's Beiträge zur Lehre vom Stoffwechsel. Berlin (1894), Heft. 2, also L. Vogel. Ueber Gicht. Zeitschr. für klin. Med., 24, 512 (1894).

[10] B. Laquer. Ueber die Ausscheidungsverhaltnisse der Alloxurkorper im Harn von Gesunden und Kranken. Verhandl. des 14t Kongr. für innere Medizin, 333 (1896).

[11] H. Vogt. Ein Stoffwechselversuch bei acute Gicht. Deutsche Arch. für klin. Med., 71, 21 (1901).

According to the experiments of Magnus-Levy,[1] the metabolism of nitrogen in gout resembles somewhat the metabolism of nitrogen in certain kidney diseases. There are alternate periods of nitrogen retention and nitrogen loss. Magnus-Levy found that the period of nitrogen loss was usually during the attack, and the period of nitrogen retention after the attack. Futcher,[2] too, found the excretion of nitrogen high during an acute attack of gout. Camerer [3] and Zagari [4] found alternate periods of nitrogen loss and nitrogen retention. According to Zagari,[4] the period of nitrogen loss is usually coincident with that of the acute attack, but not always. In one case of Laquer's,[5] the nitrogen excretion on two successive days was 5.2 grams and 22.9 grams respectively.

Both Vogel and Magnus-Levy showed that the body weight did not increase with nitrogen retention and decrease with the loss of nitrogen in these cases. Further, the quantity of food given, reckoned in calories, was in most cases about the proper quantity. In some cases the quantity given was increased or diminished, but this did not seem to affect the peculiar results. We cannot state in what form the nitrogen is retained in gout. According to Loewi, it is retained as uric acid. But Loewi [6] based this view on the erroneous assumption that the quantity of endogenous uric acid excreted per day is the same for all persons.

Watson [7] found in one case an increase in urea during an attack. Pfeiffer [8] found the urea high during an attack and low after an attack.

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[1] A. Magnus-Levy. Beiträge zum Stoffwechsel bei Gicht. Berl. klin. Wochenschrift, 33, pp. 389 and 416 (1896), also

Ibid. Ueber Gicht. Zeitschr. für klin. Med., 36, 353 (1898).

[2] T. Futcher. Some Points on the Metabolism in Gout, with Special Reference to the Relationship between the Uric Acid and the Phosphoric Acid Elimination in the Intervals and during Acute Attacks. Practitioner, Lond., 71, 181 (1903).

[3] Camerer. Beitrag zur Erforschung der stickstoffhaltigen Bestandtheile des menschlichen Urins, insbesondere des sogenannten Alloxurkörper. Zeitschr. für Biol., 35, 206 (1897).

[4] G. Zagari. Il balancio organico di un gottosa durante e fuori l'accesso. Napoli (1898).

[5] B. Laquer. Ueber die Ausscheidungsverhältnisse der Alloxurkörper im Harn von Gesunden und Kranken. Verhandl. des 14t Kongr. für innere Med., 333 (1896).

[6] O. Loewi. Beitrag zur Kenntniss des Nucleinstoffwechsels. I Mittheilung. Arch. für exp. Path. u. Pharm., 44, 1 (1901).

[7] Watson. Observations on General Metabolism and the Blood in Gout. Brit. Med. Journ. (1901), I, 10.

[8] F. Pfeiffer. Ueber die Ausscheidungen im Urin während des acuten Gichtanfalles mit besonderer Berücksichtigung der Harnsäure. Berl. klin. Wochenschrift, 33, 319 (1896).

Another peculiarity of the metabolism of gout is the great loss of nitrogen in the feces. In several cases observed by Vogel,[1] the quantity of nitrogen in the feces was from ten to fifteen per cent. as much as that in the food. This same great loss was observed in the experiments of Magnus-Levy,[2] Schmoll,[3] and Vogt,[4] except that in one of Magnus-Levy's cases the loss was only from five to eight per cent.

Kaufmann and Mohr [5] found the absorption bad in one case of gout. In three cases it was good; only five to eight per cent. of the amount of nitrogen in the food was found in the feces. Further, Kaufmann and Mohr found the P_2O_5 in the feces increased more in gout after thymus than in health, and assumed that this indicates poor absorption of nucleoproteid. This conclusion is not warranted. The amount of P_2O_5 in the feces does not depend wholly on the amount unabsorbed from the food, but on other factors; the amount of calcium in the food, for example, being one of them.

The increase in nitrogen in the feces is not necessarily due to unabsorbed food. It may be due to increased secretion or excretion in the digestive tract. The fact observed by Vogel [1] that all but about five to seven per cent. of the fat is absorbed indicates that we probably do not have a condition of poor absorption. Magnus-Levy [6] found that nine to ten per cent. of the fat of the food is left unabsorbed. This is not exceedingly high. Adler [7] has suggested that the high nitrogen content of the feces is due to intestinal fermentation. There are evidences of intestinal fermentation in gout, as we shall see.

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[1] L. Vogel. Ueber den Stoffwechsel bei Gichtkranken. Enthalten in einem Vortrag von Noorden's Beiträge zur Ernährungslehre nach Versuchen von Dr. Kayser, Krug, Dapper, Vogel. Sitzungsber. der physiol. Gesellsch., Berlin, 17 Febr., 1893; Du Bois Archiv, 377 (1893), and in von Noorden's Beiträge zur Lehre vom Stoffwechsel, Berlin (1894), Heft. 2, also

Ibid. Ueber Gicht. Zeitschr. für klin. Med., 24, 512 (1894).

[2] A. Magnus-Levy. Beiträge zum Stoffwechsel bei Gicht. Berl. klin. Wochenschrift, 33, pp. 389 and 416 (1896), also

Ibid. Ueber Gicht. Zeitschr. für klin. Med., 36, 353 (1898).

[3] E. Schmoll. Stoffwechselversuch an einem Gichtkränken. Zeitschr. für klin. Med., 29, 510 (1896).

[4] H. Vogt. Ein Stoffwechselversuch bei acute Gicht. Deutsche Arch. für klin. Med., 71, 21 (1901).

[5] M. Kaufmann und L. Mohr. Beiträge zur Alloxurkörperfrage und zur Pathologie der Gicht. Deutsche Arch. für klin. Med., 76, 586 (1902).

[6] A. Magnus-Levy. Beitrage zum Stoffwechsel bei Gicht. Berl. klin. Wochenschrift, 33, pp. 389 and 416 (1896).

[7] A. Adler. Zum Verständniss einiger gichtischer Erscheinungen. Deutsche med. Wochenschrift, 27, 86 (1901).

METABOLISM OF PHOSPHORUS, POTASSIUM, INDICAN, ETC.

The early writers disagreed concerning the metabolism of phosphoric acid in gout. According to Böcker,[1] Parkes,[2] Stokvis,[3] and Jones,[4] the P_2O_5 in the urine is low. Berthollet [5] and Scudamore [5] found it high. Lecorché [4] stated that it varies with the uric acid excretion.

According to Schmoll,[6] the excretion of P_2O_5 in gout is normal. Watson [7] found a marked diminution in the excretion of P_2O_5 during the first few days of an acute attack, followed by an equally marked increased excretion. Waldvogel [8] observed the same result.

Vogt's [9] experiments seem to indicate that when nucleins are fed to a gouty person, some of the uric acid formed from the purin is retained, whereas the P_2O_5 is immediately excreted. Ten Cate [10] and Kaufmann and Mohr [11] find that the opposite is true. When nucleins are fed, the P_2O_5 is retained and the uric acid excreted. Futcher [12] found the P_2O_5 excretion low in gout, but parallel with that of uric acid. The P_2O_5 in the urine is not a measure of the total P_2O_5 excretion. A variable amount, dependent somewhat on the quantity of calcium excreted, is found in the feces, so that we should expect somewhat discordant results.

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[1] Böcker. Zur Pathologie der Gicht. Rhein Monatsh., Feb. (1850), and Canstatts, Jahresb. (1850), 158.

[2] E. Parkes. The Composition of the Urine in Health and Disease and under the Action of Remedies. London (1860).

[3] B. Stokvis. Zur Kenntniss der Phosphorausscheidung bei Arthritis. Centralblatt für med. Wissensch., 13, 801 (1875).

[4] D. Duckworth. A Treatise on Gout. London (1890).

[5] C. Bouchard. Maladies par ralentissement de la Nutrition. Paris (1882).

[6] E. Schmoll. Stoffwechselversuch an einem Gichtkranken. Zeitschr. für klin. Med., 29, 510 (1896).

[7] G. Watson. Observations on General Metabolism and the Blood in Gout. Brit. Med. Journ., 1, 10 (1900), also

Ibid. Metabolism in Gout, with Observations on the Action of Salicylate of Soda and Nucleic Acid. Journ. of Path., 7, 103 (1901).

[8] Waldvogel. Der Stoffwechsel in Gichtanfall. Centralbl. für Stoffwechsel und Verdauungskrankheiten, 3, 1 (1902).

[9] H. Vogt. Ein Stoffwechselversuch bei acute Gicht. Deutsche Arch. für klin. Med., 71, 21 (1901).

[10] B. ten Cate. Beiträge zur gichtischen Diathese. Inaug. Dissert., Göttingen (1899).

[11] M. Kaufmann und L. Mohr. Beiträge zur Alloxurkörperfrage und zur Pathologie der Gicht. III Theil. Stoffwechselbeobachtungen bei 5 Gichtkranken. Deutsche Arch. für klin. Med., 74, 586 (1902).

[12] T. Futcher. Some Points on the Metabolism in Gout, with Special Reference to the Relationship between the Uric Acid and the Phosphoric Acid Elimination in the Intervals and during Acute Attacks. Practitioner, 71, 181 (1903).

Soetbeer [1] found the excretion of potassium in two cases of gout low, compared with that in two healthy persons living on the same diet.

Magnus-Levy [2] found the indican in the urine enormously increased in gout, an indication of intestinal fermentation. Grossman [3] found the indican rather low in gout on a milk diet. The significance of this is probably important from a chemical standpoint, for some observers have found good clinical results from milk diet in gout.

Hall [4] found the excretion of aromatic sulphates high in gout. This is considered an indication of intestinal putrefaction.

According to Ebstein [5] and others, glycosuria occurs often in gout.

We will conclude this sketch of the metabolism in gout with a brief summary of the important points.

Concerning the metabolism of uric acid, we may say that the excretion of uric acid gradually increases for a few days after the onset of an acute attack of gout and then gradually decreases to normal.

Different authors disagree concerning the effect of nucleins on the excretion of uric acid in gout. Some have found the excretion of uric acid increased after purin food. Others have confirmed this, but stated that the increase was not so marked as in health. Soetbeer, who appears to have done careful work, found absolutely no increase in the excretion of uric acid after purin food in gout in some cases. In view of the fact that digestive disturbances are very marked in gout, the differences may possibly be due to differences in absorption, or the purin may be destroyed before absorption.

The relation between the purin bases and uric acid in the urine in gout is normal.

The metabolism of nitrogen is abnormal. There are alternate periods of nitrogen retention and nitrogen loss, as in nephritis, without corresponding changes in the body weight. According to Magnus-Levy, the periods of nitrogen loss are coincident with those

[1] F. Soetbeer. Ein Stoffwechselversuch bei Gicht. Zeitschr. für physiol. Chem., 40, 55 (1903).

[2] A. Magnus-Levy. Ueber Gicht. Zeitschr. für klin. Med., 36, 353 (1898).

[3] J. Grossman. Zur Kenntniss des Harnsäurestoffwechsels und des Harnindicans bei Gichtkranken. Berl. klin. Wochenschrift, 40, 539 (1903).

[4] I. Hall. Metabolism in Gout and the Need for Combined Investigation. Practitioner, 71, 61 (1903).

[5] W. Ebstein. Angina Pectoris neben Arthritis uratica und Diabetes mellitus. Berl. klin. Wochenschrift, 32, 493, 522 and 545 (1895).

of acute attacks, and the nitrogen retention occurs during convalescence. Other experimenters observed nitrogen retention during acute attacks of gout. The feces are usually very high in nitrogen, though according to Kaufmann and Mohr, this is not always the case. The absorption of fat is good, and probably, therefore, according to Vogel, the absorption of proteid is good, so that the large amount of nitrogen in the feces is due to excretion of nitrogen into the intestines, or comes from the walls of the intestines.

The results obtained by different authors in the study of the metabolism of phosphorus are contradictory. While some find a retention of P_2O_5 after nuclein feeding, others find the P_2O_5 excreted just as in normal persons.

It is plain that there is much to be learned concerning the metabolism in gout. We hope to study the nitrogen absorption and the metabolism of uric acid and phosphorus on both nuclein food and nuclein-free food.

Cause of the Increased Uric Acid in the Blood in Gout

In view of the chemical composition of gouty concretions, the fact that uric acid is found in the blood in gout but not in health seems important. We shall, therefore, examine the different theories which have been offered to explain its presence. It has been suggested that this uric acid may be due to an increased formation of uric acid, and that the kidneys cannot excrete it fast enough to free the blood of it. It has also been suggested that the uric acid is retained either because the kidneys are diseased, or because the uric acid is not combined in such a way that it can be excreted. Further, various causes might contribute to bring about a decrease in the amount of uric acid oxidized to urea. This might cause the presence of uric acid in the blood. There is another possibility. In health, uric acid may be in the blood, but combined as an organic compound in such a way as not to be detected by our usual chemical tests for uric acid. In gout the uric acid may not all be combined in this way; therefore we find it in the blood.

INCREASED FORMATION OF URIC ACID

According to Latham,[1] the primary fault in gout is one of imperfect metabolism of glycocine, whereby this is not changed to

[1] P. Latham. Some Points in the Pathology of Rheumatism, Gout, and Diabetes. (Croonian Lectures.) Lancet (1886), I, 626, 672, 723, 771, and 817.

urea, but passes into the kidney and there combines with urea to form uric acid. It is then reabsorbed and passes into the circulation. Wiener[1] likewise believes that an increase in the amount of uric acid formed by synthesis may account in part for the presence of uric acid in the blood in gout.

We have already seen that there is no evidence to show that uric acid is formed by synthesis from urea and glycogen in the body, but, on the other hand, good evidence to show that uric acid is not found in this manner.

Ord[2] believed that there is increased formation of uric acid in all parts of the body in gout. According to Levison[3] there may be increased leucolysis, and according to Pfeiffer, a rapid katabolism of the cells generally in gout. Klemperer[4] and Luthje[5] likewise think that there is an increased formation of uric acid in gout. Ebstein[6] believes that in gout there is an increased formation of uric acid from nucleins in perverse places, such as the muscles, cartilage, bone marrow, etc. He defines the uric acid diathesis as a pathological disposition of man, in consequence of which, without known functional or organic primary disturbance, more uric acid is formed than normally. None of these authors offer experimental evidence in support of their views.

We should scarcely expect the presence of uric acid in the blood to be due to increased formation alone. It would be necessary to assume also that there is a decreased power of the kidneys to excrete uric acid, for healthy kidneys can excrete far more uric acid per day than has ever been observed in cases of gout. In leukemia, three to four grams uric acid per day are sometimes found in the urine.

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[1] Hugo Wiener. Die Harnsäure in ihrer Bedeutung für die Pathologie. Ergebnisse der Physiologie von Ascher und Spiro, II Jahrgang, I Abtheilung, 411 (1903).

[2] Ord. Relation of Uric Acid to Gout. Med. Times and Gazette, 1, 233 (1874).

[3] F. Levison. Die Harnsäure als Krankheitsursache. Arch. f. Verdauungskrankheiten, 3, 478 (1898).

[4] G. Klemperer. Zur Pathologie und Therapie der Gicht. Deutsche med. Wochenschrift, 21, 655 (1895).

[5] H. Luthje. Ueber Bleigicht und den Einfluss der Bleiintoxikationen auf die Harnsäureausscheidung. Zeitschr. für klin. Med., 29, 266 (1896).

[6] W. Ebstein. Beiträge zur Lehre von der harnsäuren Diathese. Wiesbaden (1891); also

Ibid. Ueber die Stellung der Fettleibigkeit die Gicht und der Zuckerkrankheit im nosologischen System. Verhandl. der 70 Naturforscherversammlung in Düsseldorf. Abtheilung für innere Med. Deutsche med. Wochenschrift, 24, 693 (1898).

RETENTION OF URIC ACID

The theory that the kidneys are so affected in gout that they fail to excrete the uric acid as fast as it is brought to them, and thus cause retention of uric acid in the blood, has been a favorite one, and has much to support it. Garrod [1] first suggested this theory. According to this author, the kidneys are always affected in the early stages of gout, and often before any symptoms of the disease appear. He found uric acid in the blood not only in gout, but in cases of albuminuria and lead poisoning. Further, the decreased excretion of uric acid observed by Garrod in gout was an argument in favor of his theory.

For a long time it was difficult to oppose this theory. All the early experimenters, using the Heinz method of determination, found the excretion of uric acid low in gout, and Becquerel,[2] Gorup-Besanez,[3] Frerichs,[4] Dickinson,[5] Bartels,[6] Fleischer,[7] and Wagner,[8] who likewise used the Heinz method, found the excretion of uric acid low in nephritis.

Uric acid, as we have seen, has been found in the blood in kidney diseases and in cases of lead poisoning, and lead poisoning predisposes to both nephritis and gout. From Garrod's time up to the present, most of those who have devoted attention to the subject have found indications of lead poisoning in a large percentage of the cases of gout. According to Luthje,[9] who studied the subject historically as well as experimentally, lead poisoning alone may cause gout.

The frequent occurrence of cases of both kidney disease, especially contracted kidney or granular atrophy, and gout in a single individual has led some authors to believe that there is a causal

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[1] A. Garrod. Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism, and Bright's Disease. Medico-Chirurg. Trans., 31, 83 (1848), also *Ibid.* The Nature and Treatment of Gout and Rheumatic Gout. London (1859).

[2] Becquerel. Semeiotique des urines ou traité des alterations de l'urine dans les maladies suivi d'un traité de la maladie de Bright. Paris (1841), 509.

[3] Gorup-Besanez. Arch. f. physik. Heilk., 8, 712 (1849).

[4] Frerichs. Die Bright'sche Nierenkrankheit und deren Behandlung. Braunschweig (1851).

[5] Dickinson. Diseases of the Kidneys and Urinary Derangements. London (1875).

[6] Bartels. Nierenkrankheiten. Ziemssen's Handbuch der spec. Path. und Therap., 9, 1 (1877), 2d ed., p. 407.

[7] R. Fleischer. Klinische und pathologisch-chemische Beiträge zur Lehre von der Nierenkrankheiten. Deutsche Arch. für klin. Medizin, 29, 129 (1881).

[8] E. Wagner. Der Morbus Brightii. Ziemssen's Handbuch der spec. Path. und Therap., 9, 1 (1882).

[9] C. Luthje. Ueber Bleigicht und den Einfluss der Bleïntoxikation auf die Harnsäureausscheidung. Zeitschr. für klin. Med., 29, 266 (1896).

relation between the two. According to Levison,[1] no case has ever been reported in the literature of a gouty person carefully examined at autopsy in which the kidneys were normal. Luff,[2] Moore,[3] and many other observers find that a large proportion of those who have had gout show evidences of kidney disease at autopsy. Further, many observers have noted that urate concretions are frequently found at the autopsy of those who have suffered from certain forms of kidney disease. According to Kam,[4] at the time of the onset of an attack of acute nephritis, the uric acid excretion is low. It gradually increases and then on convalescence decreases to slightly below normal. This is very similar to the behavior of the uric acid in an acute attack of gout, and, if it is confirmed, will be another point in favor of the retention theory. These facts, together with the fact that uric acid is found in the blood in nephritis, lend strong support to the theory that the presence of uric acid in the blood in gout is due to kidney disease, whereby there is failure on the part of the kidneys to excrete uric acid.

All observers do not admit that there is a close clinical connection between gout and kidney disease. According to Cantani [5] and Ebstein there is usually no kidney disease in the early stages of gout. Vogt [6] maintains that there can be gout without kidney disease, for, in a case of gout where thymus was fed, the P_2O_5 from the thymus was excreted, and Fleischer [7] has shown that the P_2O_5 excretion is always low in nephritis. Futcher [8] thinks that the fact that the excretion of uric acid is highest during an acute attack argues against the view that the presence of uric acid in the

[1] F. Levison. Zur Lehre von den Pathogenese der Gicht. Zeitschr. für klin. Med., 26, 293 (1894).

[2] A. Luff. The Chemistry and Pathology of Gout. (Goulstonian Lectures.) Lancet (1897), I, 857, 942, and 1069, also

Ibid. Gout, Its Pathology and Treatment. New York (1899).

[3] N. Moore. Some Observations on the Morbid Anatomy of Gout. St. Bartholomew's Hospital Reports, 23, 289 (1887).

[4] B. Kam. Bijdrage to de kenis der urinezuur-uitscheidung. Dissert., Leiden (1898), Maly's Jahresb. über die Fortschritte der Thierchemie, 28, 573 (1898).

[5] A. Cantani. Oxalurie, Gicht, und Steinkrankheiten. Specielle Pathologie und Therapie der Stoffwechselkrankheiten. German transl. by S. Hahn (1880).

[6] H. Vogt. Ein Stoffwechselversuch bei acute Gicht. Deutsche Arch. für klin. Medizin, 71, 21 (1900).

[7] R. Fleischer. Klinische und pathologisch-chemische Beiträge zur Lehre von den Nierenkrankheiten. Deutsche Arch. für klin. Medizin, 29, 129 (1881).

[8] T. Futcher. Some Points on the Metabolism in Gout: with Special Reference to the Relationship between the Uric Acid and the Phosphoric Acid Elimination in the Interval and during Acute Attacks. Practitioner, 71, 181 (1903).

blood is due to a defect in the power of the kidneys to excrete it. There are facts which make it seem doubtful if there is a connection between gout and lead poisoning. Luthje did not find that lead has any influence on the excretion of uric acid after thymus feeding, or that there is any indication that lead poisoning causes a retention of uric acid in dogs. Levison [1] states that among one hundred and sixty-three cases of lead intoxication in Frerich's clinic in Berlin, there was not one case of real gout. Roberts [2] has suggested the name uratosis for the condition in which urates are deposited in the body. He believes that gout is not caused by lead poisoning, but that gout and plumbism are two different conditions, which have uratosis as a common symptom. Even if Roberts is right, it is still possible that the presence of uric acid in the blood in these conditions is due to an imperfect excretion by the kidneys.

The question of the relation of kidney disease to lead poisoning is chiefly a clinical one yet, and we would not profit much by a discussion of it, for many authors assume, with Garrod, that a functional disturbance in the excreting power of the kidneys precedes gout even when no organic changes can be found. It is possible that those inclined to gout are likewise prone to kidney disease, but that the presence of uric acid in the blood is due to entirely different reasons in the two cases.

Stadthagen,[3] von Ackeren,[4] Fodor,[5] Albu,[6] Magnus-Levy,[7] Schreiber,[8] Martin,[9] and Kaufmann and Mohr [10] have found the

[1] Levison. Hirsch-Virchow's Jahresb. (1882), 2, 234.

[2] W. Roberts. On the Deposition of the Crystalline Urates in the Tissues Considered as a Separate Pathological Incident, with a Suggestion for a Distinctive Name. Trans. of the Med. Soc. London, 14, 84 (1891).

[3] Stadthagen. Ueber das Vorkommen von Harnsäure im verscheidenen thierischen Organen, ihr Verhalten bei der Leukämie, und die Frage ihrer Entstehung aus den Stickstoffbasen. Virchow's Archiv, 109, 390 (1887).

[4] v. Ackeren. Ueber Harnsäureausscheidung bei einigen Krankheiten, insbesondere Morbus Brighti. Charité Annalen, 17, 206 (1892).

[5] G. Fodor. Ueber die Rolle der Harnsäure bei Nephritis. Centralblatt für innere Medizin, 16, 865 (1895).

[6] Albu. Discussion of Laquer's Article. Ueber die Ausscheidungsverhältnisse der Alloxurkörper im Harne von Gesunden und Kranken. Verhandl. des 14t Kongr. für innere Medizin, 423 (1896).

[7] A. Magnus-Levy. Discussion of Laquer's Article. Ueber die Ausscheidungsverhältnisse der Alloxurkörper im Harne von Gesunden und Kranken. Verhandl. des 14t Kongr. für innere Medizin, 423 (1896).

[8] E. Schreiber. Ueber die Härnsaure unter physiologischen und pathologischen Bedingungen. Stuttgart (1899).

[9] C. Martin. Ueber die Ausscheidungsverhältnisse der Alloxurkörper bei Nephritis. Centralblatt für innere Medizin, 29, 625 (1899).

[10] M. Kaufmann und L. Mohr. Beiträge zur Alloxurkörperfrage und zur Pathologie der Gicht. II Theil. Ueber Alloxurkörperausscheidung unter pathologischen Verhältnissen. Deutsche Arch. für klin. Medizin, 74, 348 (1902).

excretion of uric acid practically the same in nephritis as in health, and Zülzer,[1] Vogel,[2] and Rommel[3] have found it even high. Kaufmann and Mohr[4] found the endogenous uric acid normal in nephritis.

Kolisch and Dostal[5] and Fodor[6] by use of the erroneous Krüger-Wulff method, found the purin bases high and uric acid low in nephritis as in gout. By use of more accurate methods, Rommel,[3] Zulzer,[1] von Noorden,[7] Albu,[7] Magnus-Levy,[7] Ascoli,[8] and Martin[9] found the quantity of purin bases, and the ratio, *uric acid : purin bases*, normal in nephritis. Rommel, Schmoll,[10] Weintraud,[11] Kam,[12] and Zagari and Pace[13] have found that excretion of uric acid is increased after thymus feeding in nephritis.

Minkowski has suggested that in cases where uric acid is found in the blood a high content of the blood in uric acid is necessary to excrete this compound.

We have not yet enough data to decide in favor of or against the theory that the presence of uric acid in the blood in gout is due to a defect in the power of the kidneys to excrete it. We have evidence that the kidneys can excrete fairly large quantities of uric acid in nephritis and in gout. In gout, and, according to Kam, in nephritis, there are periods when the excretion of uric

[1] G. Zülzer. Ueber die Alloxurkörperausscheidung im Harn bei Nephritis. Berl. klin. Wochenschrift, 33, 72 (1896).

[2] Vogel. Krankheiten der Harnbereitenden Organ. Virchow's Handbuch der spec. Path. und Ther., 4, 2, Erlangen (1856-1865).

[3] O. Rommel. Die Ausscheidung der Alloxurkörper bei Gicht und Schrumpfniere. Zeitschr. für klin. Med., 30, 200 (1896).

[4] M. Kaufmann und L. Mohr. Beiträge zur Alloxurkörperfrage und zur Pathologie der Gicht. II. Theil. Ueber Alloxurkörperausscheidung unter physiologischen Verhältnissen. Deutsche Arch. für klin. Medizin, 74, 348 (1902).

[5] R. Kolisch und H. Dostal. Das Verhalten der Alloxurkörper in pathologischen Harnen. Wien. klin. Wochenschrift, 8, 413, and 435 (1895).

[6] G. von Fodor. Ueber das Verhalten der Harnsäure bei Nephritis. Centralblatt für innere Medizin, 16, 865 (1895).

[7] von Noorden, Albu, and Magnus-Levy in a Discussion of Laquer's Article. Ueber die Ausscheidungsverhältnisse der Alloxurkörper im Harne von Gesunden und Kranken. Verhandl. des 14t Kongr. für innere Med., 420 (1896).

[8] G. Ascoli. Sul comportamento dei corpi allosurici nelle nefriti. Clinica Med. (1898); Maly's Jahresb. über die Fortschritte der Thierchemie, 29, 722 (1899).

[9] C. Martin. Ueber die Ausscheidungsverhältnisse der Alloxurkörper bei Nephritis. Centralblatt für innere Medizin, 29, 625 (1899).

[10] E. Schmoll. Stoffwechselversuch an einem Gichtkranken. Zeitschr. für klin. Med., 29, 510 (1896).

[11] Weintraud. Zur Entstehung der Harnsäure im Säugethierorganismus. Verhandl. des 14t Kongr. für innere Med., 190 (1896).

[12] B. Kam. Bijdrage to de kenis der urinzuur-uitscheidung. Leiden (1898); Maly's Jahresb. über die Fortschritte der Thierchemie, 28, 573 (1898).

[13] G. Zagari e D. Pace. La genesi dell' acido urico e la gotta in riguardo alla patogenesi e all' indirizzo terapeutico. Napoli (1897). Centralblatt für innere Medizin, 19, 816 (1898).

acid is low and other periods when it is not. It might be assumed that there is a retention of uric acid when the excretion is low. We should then expect to find uric acid in gouty blood only at such a period. This is not in accord with the fact that uric acid has been found in the blood at all periods. The experiments of Soetbeer and others indicate that after ingestion of purin food the excretion of uric acid is not increased, or, at any rate, not so much as in health. This may be due to a lack of absorption, to the fact that the uric acid formed is oxidized to urea, that the nucleins or purin bases are not oxidized to uric acid, or that uric acid is formed, but is retained in the body or excreted in the feces. Even if there is retention of uric acid in gout, it is plain that a retention might be due to some cause other than diseased kidneys. Minkowski has suggested that the uric acid may not be chemically combined in such a way as to be in a condition to be excreted, an idea suggested by Parkes [1] long ago.

DECREASED DESTRUCTION OF URIC ACID

The old theory of Liebig [2] and Jones [3] was that uric acid is an antecedent of urea in the destructive metabolism of proteid by oxidation. According to these authors, all the urea excreted has passed through the stage of uric acid. If, for any reason, the oxidation processes of the body become defective, more of the nitrogen than normally is oxidized only to the stage of uric acid, and, therefore, less uric acid is excreted. This likewise is the theory that Ralfe [4] and Cantani [5] give in their books.

Even more recently, Rendu,[6] Murri,[7] Stekel,[8] and Halliburton [9] have stated that the formation of a large quantity of uric acid is due to a diminution of the oxidation processes.

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[1] E. Parkes. The Composition of the Urine in Health and Disease, and under the Action of Remedies. London (1860).

[2] J. Liebig. Animal Chemistry, or Organic Chemistry in its Application to Physiology and Pathology. Edited by W. Gregory, 1843.

[3] H. Bence Jones. Lectures on Some of the Applications of Chemistry and Mechanics to Pathology and Therapeutics. London (1867), also

A Treatise on Gravel, Calculus, and Gout. London (1845).

[4] C. Ralfe. Outlines of Physiological Chemistry. London (1873).

[5] Cantani. Oxalurie, Gicht und Steinkrankheiten. Berlin (1880).

[6] Rendu. Goutte. Dictionnaire usuel des sciences médicales. A. Deschambre, M. Duval, et L. Lereboullet. Paris (1885), 706.

[7] Murri. Uricämie und Gicht. Kongr. für innere Med. in Rom. Wien. klin. Wochenschrift, 3, 316 (1890).

[8] W. Stekel. Zur Pathologie und Therapie der Gicht. Wien. klin. Wochenschrift, 51, 366, 418, 474, 518 (1901).

[9] Halliburton. Essentials of Chemical Physiology (1901).

Murchison [1] believes, without proof, that in gout there is a functional derangement of the liver such that the normal process whereby albuminous matter is changed to urea is persistently deranged, and uric acid instead of urea is formed.

Croftan,[2] it will be remembered, showed that for the oxidation of uric acid in the body there is necessary an albuminose, which seems to combine with the uric acid and bring it into a condition to be oxidized, a nucleo-proteid, which acts as an oxidizing agent, or carrier of oxygen, and certain inorganic salts to hold the albuminose in solution. It might be suggested that the absence of some of these bodies might account for the presence of an increased amount of uric acid in the body.

Kochmann [3] thinks that when the liver and kidney are both diseased, and the muscles are inactive on account of very little exercise, uric acid may accumulate in the body from lack of destruction, for it seems probable that uric acid is destroyed chiefly in the liver, kidney, and muscles. According to this author, meat, alcohol, and lead lead to gout by causing degeneration in the liver and kidney.

According to Klemperer,[4] gouty blood destroys uric acid to about the same extent as healthy blood. Experiment seems to show, however, that the blood itself is an unimportant agent in the oxidation of uric acid.

Ten Cate [5] fed uric acid to a gouty patient, but did not find that it gave increased excretion of uric acid. He concluded that the uric acid is destroyed as well in gout as in health. There was no evidence that the uric acid was absorbed in the experiment of ten Cate.

Wiener,[6] Rosin,[7] and Kionka [8] are likewise of the opinion that the presence of uric acid in the blood in gout may be due to

[1] G. Murchison. Clinical Lectures on Diseases of the Liver. 3d ed., 568 (1877).

[2] A. Croftan. Synopsis of Experiments on the Transformation of Circulating Uric Acid in the Organism of Man and Animals. Med. Record, 64, 6 (1903).

[3] M. Kochmann. Ueber Fleischnahrung und ihre Beziehung zur Gicht. Pflüger's Archiv. für die gesammt. Physiol., 94, 593 (1903).

[4] G. Klemperer. Lösung und Zerstörung der Harnsäure im Blute Gesunden und Gichtkranken. Therapie der Gegenwart, Neue Folge, 3, 344 (1901).

[5] B. ten Cate. Beiträge zur gichtischer Diathese. Inaug. Dissert., Göttingen (1899).

[6] H. Wiener. Ueber Zersetzung und Bildung von Harnsäure in Thierkörper. Arch. für exp. Path. u. Pharm., 42, 375 (1899).

[7] H. Rosin. Ueber den Augenblicklichen Stand der Lehre von der Gicht. Therapeutische Monatshefte, 15, 168 (1901).

[8] H. Kionka. Entstehung und Wesen der Vogelgicht und ihre Beziehung zur Arthritis urica des Menschen. Arch. für exp. Path. u. Pharm., 44, 186 (1900).

decreased destruction of uric acid. Decreased destruction of uric acid cannot be the sole cause of the presence of uric acid in the blood. A decreased destruction of uric acid would lead merely to an increased excretion of uric acid. There is not an increased excretion of uric acid in gout, nor is there any other evidence of an increased formation of uric acid.

CHEMICAL CHANGE IN THE URIC ACID

Pfeiffer,[1] it will be remembered, found that the uric acid in the urine in gout is in what he called the "free" condition. By this he meant that it was easily given up to the uric acid filter. He assumed by analogy that the uric acid is "free" in the blood in gout, and that this is why it is found on analysis and why it is easily given up in the joints to form concretions. We have already seen the explanation of Pfeiffer's peculiar results. The foundation of his theory is wrong.

It is plain that the data we have at present are not sufficient to enable us to explain the cause of the presence of uric acid in the blood in gout.

Cause of the Formation of the Uric Acid Concretions in Gout

CHEMICAL THEORIES

Pearson,[2] Wollaston,[3] Fourcroy,[4] Holland,[5] and Cruveilhier[6] all regarded uric acid as intimately connected with gout. Forbes[7] and Parkinson[8] went further, and stated their belief that when the system or blood has so much uric acid in it that it has become saturated, a precipitation of this body in the joints takes place,

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[1] E. Pfeiffer. Harnsäureausscheidung und Harnsäurelösung. Verhandl. des 7t Kongr. für innere Medizin, 327 (1888).

Ibid. Die Natur und Behandlung der Gicht. Verhandl. des 8t Kongr. für innere Medizin, 166 (1889).

Ibid. Die Gicht und ihre erfolgreich Behandlung. Wiesbaden (1891), 2d ed.

Ibid. Ueber Harnsäure und Gicht. Berl. klin. Wochenschrift, 29, 383, 412, 461, 490, 536 (1892).

[2] G. Pearson. Philosophical Transactions (1797), pt. 2.

[3] Wollaston. On Gouty and Urinary Concretions. Philosophical Transactions, 2, 386 (1797).

[4] Fourcroy. Examen des expériences et des observations nouvelles de M. G. Pearson, etc. Annales de Chimie, 27, 225 (1798).

[5] H. Holland. Medical Notes and Reflexions (1839).

[6] Cruveilhier. Anatomie pathologique. Paris (1829).

[7] M. Forbes. A Treatise on Gravel and Gout. London (1793).

[8] J. Parkinson. Observations on the Nature and Cure of Gout. London (1805).

causing gout. Mazuyer,[1] Andral,[2] Copeland,[3] Rayer,[4] and Ure [5] all believed that in gout the precipitation of uric acid in the joints is due to the fact that the blood is saturated with it.

Andral and Copeland believed that the presence of the uric acid was due to meat eating. Copeland suggested that the kidneys are unable to excrete the excessive amount of uric acid. Mazuyer recommended alkalies for dissolving the concretions. Liebig [6] and Jones [7] had likewise believed that gout is due to the presence of an increased amount of uric acid in the system.

Toward the end of the seventeenth century, Sydenham had stated his belief that there was a "*materia peccans*" circulating in the blood in gout which caused the disease. The greater part of the physicians for the next century and a half accepted Sydenham's belief. It was this belief, together with the discovery of the presence of uric acid in the joints, that led to the idea that uric acid is the circulating "*materia peccans.*" But, until the work of Garrod, there was no proof that there is uric acid in the blood in gout. Todd,[8] indeed, writing a few years before Garrod's discovery, stated that there is probably a morbid matter circulating in the blood, but criticised Liebig's view that it is uric acid.

In view of the belief of his contemporaries concerning the connection of uric acid and gout, it is easy to understand how important the discovery of Garrod,[9] that uric acid is present in the blood in gout and that gout and kidney disease are often associated, appeared. According to Garrod,[10] the primary defect in gout is a failure on the part of the kidneys to excrete uric acid, which then becomes stored up in the blood. When, through a decrease in alkalinity, the blood becomes saturated with uric

[1] Mazuyer. Acétate d'ammoniaque employé contre l'ivresse. Arch. gén. de méd., 1 ser., Vol. II, 132 (1826).

[2] G. Andral. Précis d'anatomie pathologique. Paris (1829).

[3] Copeland. Dictionary of Practical Medicine (1834), Vol. I, Article on Blood.

[4] P. Rayer. Traité des maladies des Reins. Paris (1839), Vol. I.

[5] A. Ure. Researches on Gout. Med. Gazette, 35, 188 (1844).

[6] J. Liebig. Animal Chemistry, or Organic Chemistry in Its App ication to Physiology and Pathology. Edited by W. Gregory (1843).

[7] H. Bence Jones. Lectures on Some of the Applications of Chemistry and Mechanics to Pathology and Therapeutics. London (1867); also
A Treatise on Gravel, Calculus, and Gout. London (1845).

[8] R. Todd. Practical Remarks on Gout, Rheumatic Fever, and Chronic Rheumatism of the Joints (1843). (The Croonian Lecture for 1843.)

[9] A. Garrod. Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism, and Bright's Disease. Medico-Chirurg. Trans., 31, 83 (1848).

[10] A. Garrod. The Nature and Treatment of Gout and Rheumatic Gout. London (1859)

acid, this body precipitates in the joints. According to Garrod, uric acid is the cause of gout. Garrod bases his theory on several assumptions: (*a*) Gout is always preceded by kidney disease; (*b*) the excretion of uric acid is low in gout; (*c*) the blood is saturated with uric acid in gout; (*d*) the alkalinity of the blood is decreased in gout; (*e*) the solubility of sodium acid urate in the blood decreases as the alkalinity of the blood decreases.

We have seen that it has not been proved that gout is always preceded by kidney disease. We know that the excretion of uric acid is not low in gout or in kidney disease, that the blood is not nearly saturated with uric acid in gout, that a decrease in the alkalinity of the blood does not decrease its power of dissolving uric acid, and that the alkalinity of the blood is not decreased in gout. That Garrod's explanation of gout is true is doubtful in view of the fact that uric acid is present in the blood not only in nephritis and gout, but also in pneumonia, leukemia, and other diseases which appear to have no relation to gout. But five cases [1] of the occurrence of both gout and leukemia in the same person have been reported; two by Duckworth, and one each by Pribram, Müller, and Spitzer. Neumeister,[2] in a statement which he attributes to von Noorden, says, "The idea that presence and solution of gout is dependent on alkalinity of the blood is as much probable as to think that alcoholic drinks can dissolve the fat of the tissues, acid the calcium of the osteophytes and trichina capsule, or that through oyster shells a carcinoma can be calcified, or that by drinking of a dilute solution of $FeCl_3$ we can stop the bleeding of an artery. Besides, we know clinically the immunity of gouty nodules to alkalies. The results of both physicians do not affect these conclusions since even homeopaths get clinical cures." Roberts [3] states that he has seen gouty attacks recur when the urine has been kept persistently alkaline for a long time. Further, as Barclay [4] pointed out, we have urate concretions that cause no pain or inflammation, and there is a gouty gastritis and gouty bronchitis which is not associated with urate crystals in the affected parts.

[1] O. Minkowski. Die Gicht. Specielle Pathologie und Therapie von Nothnagel, VII, Theil III, Wien (1903), p. 212.

[2] R. Neumeister. Lehrbuch der physiol. Chem., Part 2, p. 251, Jena (1895).

[3] W. Roberts. On the Chemistry and Therapeutics of Uric Acid, Gravel, and Gout. (Croonian Lectures for 1892.) Lancet (1892), I, 1345, 1399, and II, 69, 127.

[4] A. Barclay. On Gout and Rheumatism in Relation to Disease of the Heart. London (1866).

Gardner [1] and Hood [2] long ago suggested that the uric acid in the blood may be a symptom of gout and not the cause of it.

Lecorché,[3] Charcot,[4] and Levison [5] maintain with Garrod that gout is due to the presence of excess of uric acid in the blood.

Haig [6] has proposed a very simple theory for the explanation not only of gout but of various other diseases. According to this author, if the blood is strongly alkaline, the uric acid formed from the food is kept in solution and excreted. If the blood is only slightly alkaline, the uric acid is precipitated in the joints and causes gout or rheumatism. The presence of uric acid in the blood causes all sorts of symptoms and diseases, according to Haig.

Haig has done a little experimental work on which he bases his theories, but from a small number of experiments, and by the aid of a good many unproved assumptions and doubtful logic, he has built up a very comprehensive theory. There is no need of criticising his work in detail, however. The experiments and chief assumptions on which he bases his whole theory are open to criticism. In speaking of increased or decreased excretion of uric acid, he refers to an increase or decrease in the ratio of the quantity of uric acid to the quantity of urea in the urine. We have seen that the value of this ratio has no meaning, that the quantity of uric acid and urea in the urine can be independently varied at will by regulating the diet without affecting the health. He has used inaccurate methods for the determination of uric acid and urea throughout this work. He has assumed that the quantity of uric acid in the urine varies inversely as the acidity of the urine, that the alkalinity of the blood can be directly varied by alkalies and acids given in the food, that the solubility of sodium acid urate in the blood varies with the alkalinity of the blood, — things we know to be untrue, — and that the rate of

[1] W. Gardner. On Gout: Its History, Its Causes, and Its Cure. 4th ed., London (1860).

[2] P. Hood. A Treatise on Gout, Rheumatism, and Allied Affections. London (1871).

[3] Lecorché. Traité theorique et practique de la goutte. Paris (1884).

[4] J. Charcot. Leçons sur les maladies du foie des voies biliaires et des reines. Paris (1877).

[5] F. Levison. Zur Behandlung der Gicht (Arthritis urica) und speciell von der Behandlung der chronischen Formen dieser Krankheit. St. Petersburg med. Wochenschrift, Neue Folge, 14, Nos. 1 and 9 (1897), and

Ibid. Zur Lehre von der Pathogenese der Gicht. Zeitschr. für klin. Med., 26, 293 (1894), and

Ibid. The Uric Acid Diathesis: Gout, Sand, and Gravel. Transl. by L. Scott, London (1894).

[6] A. Haig. Uric Acid as a Factor in the Causation of Disease. 3d ed., Phila. (1896).

the circulation of the blood in the capillaries is dependent on the quantity of uric acid in the blood — something for which there is no foundation. None of his conclusions, therefore, are of any value.

Luff's [1] theory is similar to that of Garrod in a general way. He assumes that kidney disease always precedes an attack of gout. The kidneys both form and excrete uric acid. When they are diseased the uric acid formed is reabsorbed by the blood. It circulates in the blood as a quadriurate which easily changes to a soluble gelatinous form of biurate. If this gelatinous biurate is not rapidly excreted, it changes to the insoluble crystalline biurate. A decrease in the alkalinity of the blood does not affect the solubility of the urate.

It has not been proved that kidney disease always precedes gout. Luff does not offer sufficient evidence to show that uric acid is formed in the kidneys. We know that the quadriurate does not exist, and we know that the blood is not saturated with uric acid in gout. Luff's theory, therefore, cannot be correct.

According to Ebstein,[2] uric acid circulates in the blood as a neutral urate. In gout there is an increased formation of uric acid in perverse places, such as the muscles, cartilage, and bone marrow. When for some reason there is a stasis of the blood or lymph stream containing an increased quantity of urate, there occurs an infiltration of the tissues in the circumscribed area by the lymph containing the dissolved urate. This compound is a poison and causes necrosis of the surrounding tissue. In the process of necrosis a free acid is formed which changes the neutral urate to insoluble acid urate and this latter precipitates out. Schreiber,[3] who repeated the experiments of Ebstein, and apparently confirmed them, agrees with Ebstein.

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[1] A. Luff. The Chemistry and Pathology of Gout. (Goulstonian Lectures.) Lancet (1897), I, 857, 942, and 1069.

Ibid. The Pathology and Treatment of Gout. Brit. Med. Journ. (1898), 1, 150.

Ibid. Gout: Its Pathology and Treatment. New York (1899).

Ibid. The Gelatinous Form of Sodium Biurate and Its Bearing on the Pathology and Treatment of Gout. Brit. Med. Journ. (1899), II, 1163.

Ibid. The Gelatinous Form of Sodium Biurate and Its Bearing on the Pathology and Treatment of Gout. Brit. Med. Journ. (1900), I, 836.

[2] W. Ebstein. The Regimen to be Adopted in Cases of Acute Gout. Transl. by Scott, London (1885), and

Ibid. Beiträge zur Lehre von der harnsäuren Diathese. Wiesbaden (1891).

[3] E. Schreiber. Gicht. Ueber die Harnsäure unter physiologischen und pathologischen Bedingungen. Stuttgart (1899), and

E. Schreiber und Zaudy. Ueber die bei Vögeln kunstlich zu erzeugenden Harnsäure-Ablagerungen. Pflüger's Archiv, 79, 53 (1900).

Neutral urates exist only in solutions which are strongly alkaline, with such a base as NaOH. They cannot exist in a solution containing carbonates. Ebstein is, therefore, wrong in believing that uric acid exists in the blood as neutral urate. There is no proof that in gout there is a formation of uric acid in anomalous places. The stasis and infiltration of surrounding tissue assumed by Ebstein is not at all proved. Experiment shows that uric acid and acid urates are not toxic, or are only very slightly toxic. We cannot assume that the small quantity present in the blood in cases of gout can produce a necrosis.[1] We know that just before an attack of gout there are no apparent toxic symptoms, although the blood contains uric acid.[2] Sodium acid urate, the form in which uric acid is found in gouty concretions, cannot exist in the presence of a free acid. It is changed to uric acid. Further, the evidence seems to show that the tissue change is not a process of necrosis. Mordhorst [3] found that the modified tissue — degenerated tissue, according to this author — reacts not acid but alkaline. Finally, we have sufficiently good evidence to show that the urate deposits in healthy tissue. The truth of all these statements has been shown in earlier parts of this work. Ebstein's theory must, therefore, be almost entirely wrong.

A part of these objections apply also to the theories of Klemperer [1] and von Noorden,[4] for both of these authors assume that the necrosis precedes the deposition of the urate in gout. According to Klemperer, the necrosis is due to some unknown "gichtstoff." According to von Noorden, the formation and deposition of the urate is due to the activity of a ferment.

Mordhorst [5] believes that uric acid circulates in the form of a suspension of "kugel" urates containing variable quantities of alkali. In gout the quantity of urate in the blood is increased and the alkalinity and the temperature decreased. These conditions lead to a precipitation of the spherical or amorphous urates

[1] G. Klemperer. Zur Pathologie und Therapie der Gicht. Vortrag in der Verein für innere Med. zu Berl. Deutsche med. Wochenschrift, 21, 655 (1895).

[2] F. Levison. The Uric Acid Diathesis: Gout, Sand, and Gravel. Transl. by L. Scott. London (1894).

[3] Mordhorst. Zur Entstehung der Uratablagerung bei Gicht. Virchow's Archiv, 148, 285 (1897).

[4] C. v. Noorden. Lehrbuch der Pathologie des Stoffwechsels. Berlin (1893).

[5] C. Mordhorst. Zur Pathologie der Gicht. Verhandl. des 14t Kongr. für innere Medizin, (1896), 405, also

Ibid. Die Entstehung und Auflösung Harnsäureverbindungen ausserhalb und innerhalb des menschlichen Körpers. Zeitschr. für klin. Med., 22, 65 (1897).

which gradually become crystalline. The precipitation takes place in the cartilage on account of the fact that the blood supply is poor, and the cartilage is therefore nourished chiefly by osmosis. Acids and acid salts diffuse more rapidly than alkalies or alkaline salts.

We have seen that urates such as Mordhorst speaks of, containing a variable quantity of alkali, do not exist, that the alkalinity of the blood is not decreased, and that the blood is not saturated with uric acid in gout.

We have already seen that Kolisch,[1] and more recently Croftan,[2] are in error in their view that the fault in gout lies in formation of too little uric acid and too large quantity of toxic purin bases.

According to Pfeiffer,[3] the uric acid in the blood in gout is in such a condition that it easily precipitates, just as the uric acid easily precipitates from the urine in gout. This author believes that the uric acid deposits only in tissue which is necrosed.

We must remember, as Liebreich [4] pointed out, that the deposit in the joints is not uric acid as in urine, but sodium acid urate. Further, we have seen that Pfeiffer's experimental work is open to criticism, and the conclusions he drew from his work were erroneous. Finally, necrosis does not precede the formation of the urate concretions.

Roberts [5] called attention to the fact that the tissues in which the urate deposits are chiefly found, the cartilage, ligaments, and tendons, and the synovia in which these tissues are bathed, are richer in sodium salts than other parts of the body. We know

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[1] R. Kolisch. Ueber Wesen und Behandlung der Gicht. Wien. klin. Wochenschrift, 8, 787 (1895), also

Ueber Wesen und Behandlung der uratischen Diathese. Stuttgart (1895), and

R. Kolisch und Dostal. Das Verhalten der Alloxurkörper im pathologischen Harn. Wien. klin. Wochenschrift, 8, 413, and 435 (1895).

[2] A. Croftan. An Investigation into the Causes of So-Called Uric Acid Lesions and a Rational Therapeutics of the Uratic Diathesis. N. Y. Med. Journ., 72, 221 (1900).

[3] E. Pfeiffer. Harnsäureausscheidung und Harnsäurelösung. Verhandl. des 7t Kongr. für innere Medizin, Wiesbaden (1886), 444.

Ibid. Die Natur und Behandlung der Gicht. Verhandl. des 8t Kongr. für innere Medizin (1889), 166.

Ibid. Die Gicht und ihre erfolgreich Behandlung. Wiesbaden (1891), 2d ed.

Ibid. Ueber Harnsäure und Gicht. Berl. klin. Wochenschrift, 29, 383, 412, 461, 490, and 536 (1892).

Ibid. Ueber die Ausscheidung im Urin während des acuten Gichtanfalles mit besonderer Berücksichtigung der Harnsäure. Berl. klin. Wochenschrift, 33, 319 (1896).

[4] Liebreich. In Discussion of Article by Pfeiffer. Harnsäureausscheidung und Harnsäurelösung. Verhandl. des 17t Kongr. für innere Medizin, 337 (1888).

[5] W. Roberts. On the Chemistry and Therapeutics of Uric Acid, Gravel, and Gout. (Croonian Lectures for 1892.) Lancet (1892), I, 1345, 1399, and II, 69, 127.

that the presence of sodium salts decreases the solubility of sodium acid urate. According to Roberts, the synovia becomes saturated with sodium acid urate at a much lower concentration of urate than the blood, and precipitates in the surrounding tissue. He found the synovia of stall-fed animals who got little exercise much richer in sodium salts than that of animals that had plenty of exercise, and thought the fact might be of some importance in the etiology of gout. Experiment showed that if the tarsal bones of a pig are immersed in a solution of sodium acid urate, a deposition of crystals of sodium acid urate in the substance of the tissue takes place. The crystals are firmly imbedded and cannot be removed by rubbing with a nail brush. Freudweiler[1] is inclined to think that the salts may cause the precipitation of urates.

We know that Roberts is wrong in his belief that uric acid exists in the blood as quadriurate, and that this changes to the biurate and precipitates in gout, for we have seen that the quadriurate does not exist. We have no direct evidence that Roberts is wrong in his belief that the formation of concretions is due to a precipitation from a saturated solution. But here again comes up the question of why there are no urate concretions in cases of leukemia, pneumonia, etc., where the blood contains uric acid.

Various other theories, or rather guesses without any experimental basis, have been offered concerning the cause of the formation of gouty concretions. Thus, according to Ewich,[2] the uric acid circulates in the blood as such. It sometimes reacts with the Na_2CO_3 to form sodium acid urate, and this urate precipitates in the joints. According to this theory, sodium acid urate must be less soluble than uric acid, something we knew to be untrue. According to Ritter,[3] an increase in the acid sodium phosphate in the blood will bring about a precipitate of sodium acid urate. We know that this cannot be so even if we assume that the acid phosphate is not neutralized. Ritter drew his conclusions from his experiments on the urine where the precipitate is uric acid and not urate. According to Bunge,[4] the uric acid may circulate in the blood as an easily soluble compound with some organic

[1] M. Freudweiler. Experimentelle Untersuchungen über die Entstehung der Gicht. Deutsche Arch. für klin. Medizin, 68, 155 (1900).

[2] Ewich. Die Natur und Behandlung der Gicht auf dem 8t Kongr. für innere Medizin, Nebst Bemerkungen zum Correferat. Deutsche med. Wochenschrift, 15, 774 (1889).

[3] A. Ritter. Ueber die Bedingungen für die Entstehung der Harnsedimente; ein Beitrag zur Theorie der Gicht. Zeitschr. für Biol., 35, 155 (1897).

[4] Bunge. Lehrbuch der physiologischen und pathologischen Chemie. Leipzig (1902).

substance. This compound may be broken up in the organism by a ferment in gout and give the urate. Bowlby [1] thinks that the urate concretions come from a disintegration of the cartilage itself, and Roose [2] that they are due to a functional disorder of the liver. These are, of course, merely guesses.

Gore [3] and Hutchinson [4] believe that gout is an autointoxication due to poisons formed in the alimentary canal. We know that there are digestive disturbances in gout, and there are indications of intestinal fermentation. Hutchinson [4] states that the uric acid comes from the destruction of leucocytes which are formed in large quantities to repel some toxic action.

Minkowski [5] states that we can probably conclude that there is abnormal nuclein metabolism; whether of exogenous or endogenous nuclein we cannot say. It is possible, according to him, that the uric acid formed from the nuclein is not combined in such a way that it can properly pass through the body and undergo its normal metabolism.

NERVOUS THEORIES

From the time of Stahl, who was a contemporary of Sydenham, there have been physicians who have believed that the humoral theories are wrong and that gout is a disease of nervous origin. In the present century, Cullen,[6] Wells,[7] Liveing,[8] Ord,[9] Paget,[10] Meldon,[11] Latham,[12] Ewart,[13] and Duckworth [14] have emphasized

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[1] A. Bowlby. Surgical Pathology and Morbid Anatomy. London (1887).

[2] R. Roose. Gout and Its Relation to Diseases of the Liver and Kidneys. London (1887), 3d ed.

[3] W. Gore. The Origin of Gout. Brit. Med. Journ. (1900), II, 898.

[4] W. Hutchinson. The Meaning of Uric Acid and the Urates. Lancet (1903), I, 288.

[5] O. Minkowski. Die Gicht. Nothnagel's Specielle Pathologie und Therapie. Bd. VII, Th. III (1903), Wien.

[6] W. Cullen. First Lines of Practice of Physic, Vol. II, Chap. 14, Phila. (1861).

[7] S. Wells. Practical Observations on Gout, etc. (1859).

[8] E. Liveing. On Megrim, Sick Headache, and Some Allied Disorders. London (1873).

[9] Ord. On the Relation of Gout to Uric Acid. St. Thomas's Hospital Reports, 3, 227 (1873).

[10] J. Paget. Clinical Lectures and Essays. London (1875)

[11] A. Meldon. Pathology and Treatment of Gout. Brit. Med. Journ. (1881), I, 466.

[12] P. Latham. Some Points on the Pathology of Rheumatism, Gout, and Diabetes. (Croonian Lectures.) Lancet (1886), I, 626, 673, 723, 771, and 817.

[13] W. Ewart. Gout and Goutiness and Their Treatment. London (1896).

[14] D. Duckworth. A Plea for the Neurotic Theory of Gout. Brain, III, 1 (1880).

Ibid. On Lead Impregnation in Relation to Gout. St. Bartholomew's Hospital Reports, 17, 249 (1881).

Ibid. On Gout Considered as a Tropho-neurosis. Brit. Med. Journ. (1881), 1, 463.

Ibid. A Treatise on Gout. London (1890).

Ibid. The Pathology of Gout (1900), II, 571.

the importance of the nervous system in the production of gout. They have not, as a rule, had very definite notions of the rôle of the nervous system in causing gout, and their evidence has not generally been exceedingly good.

According to Latham, gout is a primary neurosis, but uric acid is the toxic agent.

In his earlier writings, Duckworth calls gout a tropho-neurosis, and says that it is characterized by " a special morbid evolution of nerve force." He thinks that some part of the medulla oblongata is specially involved. What Duckworth really meant was that gout is due to faulty metabolism, and this is what he says in his recent writings. There is no structural defect in the nervous system according to this author.

It is plain that no definite explanation of gout has yet been given that is correct. We know that in gout there is uric acid in solution in the blood, and that there are urate concretions in the joints. We do not know which of these conditions is cause or which effect, or even whether they are related as cause and effect. They may both be due to a common cause. We have criticised all the explanations that have been offered to explain gout, and have not stated any theory of our own. We are justified in this. More data is necessary concerning the metabolism in gout before we are warranted in offering any definite theory of the cause of gout. The humoral theory of gout, as expressed by Minkowski, and the nervous theory, as expressed by Duckworth, approach each other in the indefinite view that gout is due to some sort of faulty metabolism. This is as near a correct theory of gout as we have so far attained. The view of Watson,[1] that gout is a disease of bacterial origin, may be mentioned for the sake of completeness. His evidence is not convincing.

Cause of the Acute Attack of Gout

According to Garrod,[2] the acute attack of gout is due to a temporary defect in the kidneys to excrete uric acid, whereby this compound accumulates in the blood, and a temporary decrease in the alkalinity of the blood, which causes the uric acid in the blood to precipitate. The pain is due to the mechanical irritation of the sharp urate crystals.

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[1] C. Watson. Observations on the Pathogenesis of Gout. Brit. Med. Journ. (1904), 68.
[2] A. Garrod. The Nature and Treatment of Gout. (1895.)

Levison [1] agrees with Garrod in the view that an acute attack of gout is due to the deposition of urates from saturated solution in the blood. When the urates are deposited slowly, we get chronic gout. Kittel,[2] too, takes the view that the pain in gout is due to the pressure of the sharp urate crystals, and that when these concretions are slowly formed there is no pain.

Senator,[3] Rindfleisch,[4] and Roberts [5] agree with Garrod that the pain in gout is due to the mechanical irritation of the urate crystals.

According to Jones,[6] an attack of gout is a chemical process of oxidation set up in the place where the urates are accumulated, whereby the urate is oxidized further to urea and carbonates.

Ebstein [7] thinks the acute attack is due primarily to a stasis of the lymph stream containing urate in solution. This compound is toxic, and causes tissue necrosis. The necrosed tissue reacts acid and causes a precipitation of the acid urate.

Pfeiffer [8] and Aronsohn [9] believe that the deposition of urate precedes the acute attack of gout. The latter is due to the resolution of the urate on account of a temporary increase in the alkalinity of the blood.

We have already discussed the evidence on which these authors base their theories, so that it will not be necessary to show again at this place that they are wrong. We have seen that the blood alkalinity is normal in gout, at least according to titration methods, and we know that an increase in the alkalinity would not make the blood a better solvent for sodium acid urate.

We cannot state positively that the pain in gout is not due, at least in part, to the action of uric acid as a mechanical irritant.

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[1] F. Levison. The Uric Acid Diathesis. Transl. by L. Scott. London (1884).

[2] M. Levison. Die gichtischen harnsäuren Ablagerungen im menschlichen Körper. Leipzig (1902), 3 Aufl.

[3] Senator. Gicht. Ziemssen's Handbuch der speciellen Pathologie und Therapie. Leipzig (1875).

[4] Rindfleisch. Lehrbuch der pathologischen Gewebelehre. Leipzig (1873). 3 Aufl.

[5] W. Roberts. On the Chemistry and Therapeutics of Uric Acid, Gravel, and Gout. (Croonian Lectures for 1892.)

[6] H. Jones. Lectures on Some of the Applications of Chemistry and Mechanics to Pathology and Therapeutics. London (1867).

[7] W. Ebstein. Beiträge zur Lehre von der harnsäuren Diathese. Wiesbaden (1891).

[8] E. Pfeiffer. Die Gicht und ihre erfolgreich Behandlung. Wiesbaden (1891), 2 Aufl.

[9] E. Aronsohn. Zur Natur und Behandlung der Gicht und über die Bedeutung der Emser Wilhelmsquelle. Deutsche med. Wochenschrift, 16, 381 (1890).

According to Freudweiler [1] and His,[2] it has also a slight toxic action. The pain may not be due entirely to uric acid.

Hutchinson,[3] Duckworth,[4] and von Noorden [5] have maintained that urate concretions are not always found in persons who have suffered from an acute attack of gout, and that, therefore, the pain and inflammation in the attack is not due to the urate. His [2] and Freudweiler [1] have shown that the urate may be removed by phagocytes. Hutchinson, Duckworth, and von Noorden may have drawn their conclusions from the observation of cases where the urates had been removed in this manner.

Minkowski has suggested that the nucleic acid of the phagocytes may dissolve the uric acid. The increase in the excretion of uric acid after the onset of an acute attack of gout may be due to the uric acid which is dissolved by the phagocytes and excreted.

It is plain that we have not the data to explain the cause of the acute attack of gout any more than we have to explain the formation of the concretions.

Uric Acid Infarcts

Concretions containing uric acid are often found in the kidneys of children who die during the first two weeks of life. Ebstein [6] believed the uric acid to be in the form of sodium acid urate. According to Flensburg,[7] the concretions contain ammonium urate. Reusing [8] came to the conclusion that the uric acid is present as such, and not in the form of a salt.

The occurrence of these infarcts is so frequent that they are not considered pathological by some writers. Salomonsen [9] found

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[1] M. Freudweiler. Experimentelle Untersuchungen über die Entstehung der Gichtknoten. Deutsche Arch. für klin. Medizin, 68, 155 (1900).

[2] W. His. Die Ausscheidung von Harnsäure im Urin der Gichtkranken mit besonderer Berücksichtigung der Anfallzeiten und bestimmter Behandlungsmethoden. Deutsche Arch. für klin. Medizin, 65, 156 (1900), and

Ibid. Schicksal und Wirkungen des säuren harnsäuren Natrons im Bauch- und Gelenkhöhle der Kaninchen. Deutsche Arch. für klin. Medizin, 67, 81 (1900).

[3] J. Hutchinson. On the Relation which Exists between Gout and Rheumatism. Trans. Internat. Med. Congr., London, II, 92 (1881).

[4] D. Duckworth. A Treatise on Gout. London (1890).

[5] C. von Noorden. Lehrbuch der Pathologie des Stoffwechsels. Berlin (1893).

[6] W. Ebstein. Die Natur und Behandlung der Harnsteine. Wiesbaden (1884).

[7] C. Flensburg. Studier öfver Urinsyreinfarkten, urinsedimentet och albuminurin hos nyfödela. Nord. med. Arkiv. (1894), No. 9 and No. 14. Centralblatt für innere Medizin, 15, 965 (1894).

[8] H. Reusing. Beiträge zur Physiologie des Neugebornen. Zeitschr. für Geburtshülfe, und Gynäkologie, 33, 36 (1895).

[9] Salomonsen. Urinsyreinfarcthos Nyfödte. Dissert., Copenhagen (1859).

uric acid infarcts in 140 cases, and no infarcts in 160 cases, out of 304. According to Spiegelberg,[1] infarcts are found in more than half the children dying under two weeks of age. Flensburg[2] studied twenty cases and found infarcts in every case.

In accord with the old view, the infarcts were looked upon as indicating low oxidation processes in the first few days of life whereby less urea and more uric acid are formed than normally.[3] They are now generally considered simply the result of precipitation from urine which is highly concentrated in uric acid. Thus Martin and Ruge,[4] Flensburg,[2] Schreiber,[5] Reusing,[6] Mares,[7] and Sjoquist[8] found the excretion of uric acid very high in the first few days of life. Mares found that $\frac{7}{5}$ per cent of the total nitrogen of young infants is excreted as uric acid. This fraction is only $\frac{1}{2}$ per cent in adults. Reusing found the ratio of uric acid to urea from 1 : 1.5 to 1 : 6.5 during the first few days of life, an exceedingly high ratio. This author likewise called attention to the fact that the infarcts were more common in children naturally fed than in those fed artificially. The latter get much more fluid, and therefore the urine is not so likely to become saturated with uric acid. The quantity of urine excreted in twenty-four hours increases rapidly with age during the early days. The uric acid excretion is nearly stationary for a while.

The uric acid excreted by infants is endogenous uric acid. There are no purins in milk food. As we should expect, the amount excreted does not vary with the quantity of food, according to Reusing. Schreiber believes with Horbaczewski that the

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[1] H. Spiegelberg. Ueber den Harnsäureeinfarct der Neugebornen. Arch. für exp. Path. u. Pharm., 41, 428 (1898).

[2] C. Flensburg. Studier öfver Urinsyreinfarkten, urinsedimentet och albuminurin hos nyfödela. Nord. med. Arkiv. (1894), No. 9 and No. 14. Centralblatt für innere Medizin, 15, 965 (1894).

[3] Vierordt. Physiologie des Kindesalters in Gerhard's Handbuch der Kinderkrankheiten, IV, 374.

[4] Martin und Ruge. Zeitschr. für Geburtshülfe und Frauenkrankheiten, 1, 273 (1875).

[5] E. Schreiber. Gicht. Ueber die Harnsäure unter physiologischen und pathologischen Bedingungen. Stuttgart (1899).

[6] H. Reusing. Beiträge zur Physiologie des Neugebornen. Zeitschr. für Geburtshülge und Gynäkologie, 33, 1 (1895).

[7] F. Mares. Sur l'origine de l'acide urique chez l'homme. Arch. slaves de biologie, III, 207 (1888), also Centralblatt für die med. Wissenschaften, 26, 2 (1886).

[8] J. Sjoquist. Några analyser öfvers quäfrets fördelning på urinsäurne urinsyra och ammoniak i urinen hos nyfödde barn. Nord. Med. Arkiv. (1894); Maly's Jahresb. über die Fortschritte der Thierchemie, 23, 245 (1893).

high uric acid in young infants may be connected with the large amount of leucocytes in the blood at this time, but this has not been proved.

Uric Acid in Diseases other than Gout

We have already spoken of the uric acid in the blood in different diseases, so that it will not be necessary to refer to that point. We have likewise given an account of the relation between uric acid in the urine in nephritis, leukemia, lead poisoning, liver cirrhosis, and atrophy, and phosphorus poisoning. Haig's erroneous theories of the relation between uric acid and a great many diseases have been shown to have no basis. The determination of uric acid by the Heinz and Haycraft methods, and the determination of the purin bodies by the Krüger-Wulff method, gives erroneous results. We shall not, therefore, consider results determined by these methods. There have been a great many determinations of the uric acid in diseases other than gout, but when we restrict our discussion in the manner indicated in this paragraph, very few determinations are left. The results in any case do not mean much, for in practically none of the cases has the diet been regulated, and we know that the exogenous uric acid can vary greatly in amount.

In pneumonia, the excretion of uric acid has been found rather high by Kühnau,[1] Baftalowsky,[2] and Dunin and Nowaczek.[3] Kaufmann and Mohr [4] found the endogenous uric acid high.

The old view that the uric acid excretion is decreased in diabetes must be erroneous. Only Camerer [5] has found decreased uric acid excretion by an accurate method, and the variation from normal was but little. Gaethgens,[6] Ebstein,[7] Startz,[8] Bischofswerder,[9] and

[1] N. Kühnau. Experimentelle und klinische Untersuchungen über das Verhaltniss der Harnsäureausscheidung zu der Leukocytose. Zeitschr. für klin. Medizin, 28, 534 (1895).

[2] B. Baftalowsky. Richter. Ueber Harnsäureausscheidung und Leukocytose. Zeitschr. für klin. Medizin, 27, 290 (1895).

[3] T. Dunin und St. Nowaczek. Ueber Harnsäureausscheidung bei croupöser Pneumonie. Zeitschr. für klin. Medizin, 32, 1 (1897).

[4] M. Kaufmann und L. Mohr. Beiträge zur Alloxurkörper und zur Pathologie der Gicht. II Theil. Ueber Alloxurkörperausscheidung unter pathologischen Verhältnissen. Deutsche Arch. für klin. Medizin, 74, 348 (1902).

[5] Camerer. Der Gehalt des menschlichen Urins an stickstoffhaltigen Körpern, seine Acidität: die Acidose bei der Urinanalyse. Tübingen (1901).

[6] Gaethgens. Ueber Kreatinin und Harnsäureausscheidung in einem tödlich endenden Fall von Diabetes Mellitus. Med. Chem. Untersuchungen von Hoppe-Seyler, Heft 3.

[7] W. Ebstein. Zuckenharnruhs. Wiesbaden (1887).

[8] Startz. Ueber Harnsäureausscheidung bei Diabetes Mellitus. Freiburger Dissert. (1891).

[9] Bischofswerder. Dissert., Bonn (1896).

Jacoby [1] have found the uric acid excretion high. It is possible that some of these results depend upon the fact that the diabetic diet is rich in meat, which, as we know, contains purin bodies. Kaufmann and Mohr [2] found the endogenous uric acid high in diabetes.

Baftalowsky [3] found the uric acid excretion rather high in phthisis, and Camerer [4] found it high in a case of acute miliary tuberculosis. Brandeburg [5] and Kühnau and Weiss [6] found normal uric acid excretion in tuberculosis. Topfer [7] found it sometimes high and sometimes low.

Baftalowsky [3] found high uric acid excretion in typhus. Kühnau and Weiss [6] found it normal.

The results of Topfer [7] and Kühnau and Weiss [6] show increased excretion of uric acid in anemia. Brandeburg [5] obtained normal results.

Topfer [7] found rather low uric acid excretion in cases of cancer. Pott [8] found normal uric acid excretion in cases of cancer of the stomach and of the breast.

According to Blumenthal,[9] the uric acid excretion in whooping cough is two to three times as high as in health.

Sticker [10] found the uric acid excretion high in hay fever.

Kühnau [11] obtained high results on the days of high temperature in tertiary intermittent fever.

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[1] M. Jacoby. Ueber die Ausscheidung der stickstoffhaltigen Bestandtheile beim Diabetes Mellitus. Zeitschr. für klin. Med., 32, 557 (1897).

[2] M. Kaufmann und L. Mohr. Beiträge zur Alloxurkörper und zur Pathologie der Gicht. II Theil. Ueber Alloxurkörperausscheidung unter pathologischen Verhältnissen. Deutsche. Arch. für klin. Medizin, 74, 348 (1902).

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[5] W. Brandeburg. Ueber die diagnostiche Bedeutung der Harnsäure und Xanthinbasen im Urin. Berl. klin. Wochenschrift, 33, 137 (1896).

[6] W. Kühnau und F. Weiss. Weitere Mittheilungen zur Kenntniss der Harnsaüreausscheidung bei leukocytose und hypoleukocytose sowie zur Pathologie der Leukämie. Zeitschr. für klin. Med., 32, 482 (1897).

[7] G. Topfer. Ueber die Relationen der stickstoffhaltigen Bestandtheil im Harne bei Carcinom.

[8] R. Pott. Stoffwechselanomalien bei einem Fall von Stauungsicterus. Pflüger's Archiv, 46, 509 (1890).

[9] F. Blumenthal. Ueber einige Eigenschaften des Harns bei Keuchhusten. Petersburger med. Wochenschrift (1893), Beilage 3; Maly's Jahresb. über die Fortschritte der Thierchemie, 23, 546 (1893).

[10] Sticker. Der Bostock's Sommerkatarrh (Heufieber). Nothnagel's Handbuch (1896), 4, 1, 108.

[11] Kühnau. Ueber das Verhalten des Stoffwechsels und der weissen Blutelemente bei Blutdissolution. Deutsche Arch. für klin. Medizin, 58, 344 (1897).

Beck [1] found normal values for the uric acid excretion in osteomalacia.

Colasanti [2] has confirmed the experiments of Marchand,[3] Lehmann,[4] and Rayer,[5] showing the presence of uric acid in the vomitus in cases of hysterical anuria.

Mandel [6] found some relation between the quantity of purin bases in the urine and the temperature in fever, and suggested that these may help to bring about the fever.

It will be well to state here that there has never been shown any relation between uric acid and rheumatism. Haig believed that gout and rheumatism are the same disease and due to uric acid. Mort believed that the difference between these two diseases is that in gout crystalline uric acid is deposited in the joints, and that in rheumatism his so-called "kugel" or amorphous spherical urates are deposited. We have seen that the evidence offered by these authors is of no value.

It is generally supposed that there is a relation between certain nervous diseases and uric acid. The idea is based on the experiments of Haig, Ferguson,[7] Krainski,[8] and Caro,[9] who found the amount of uric acid excreted proportional to the severity of the attack in epilepsy; to the experiments of Herter and Smith,[10] who found the uric acid excretion high in severe cases of neurasthenia, and to the experiments of Lange,[11] who found mental depression associated with high uric acid in the blood. Haig, Ferguson, and Krainski used the inaccurate Haycraft method in determining uric acid, and Caro used the

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[8] N. Krainski. Untersuchungen über den Stoffwechsel bei Epileptikern und zur Pathologie der Epilepsie. Maly's Jahresb. über die Fortschritte der Thierchemie, 26, 770 (1896).

[9] Caro. Ueber die Beziehung epileptischen Anfälle zur Harnsäureausscheidung. Deutsche med. Wochenschrift, 26, 308 (1900).

[10] C. Herter and E. Smith. Observations on the Excretion of Uric Acid in Health and Disease. N. Y. Med. Journ., 55, 617 (1892).

[11] Lange. Om Periodiske Depressionstilstande. Cobenhaven (1886).

Heinz method. Levison [1] has repeated the work of Lange and found no relation between uric acid in the blood and epileptic attacks.

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END

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